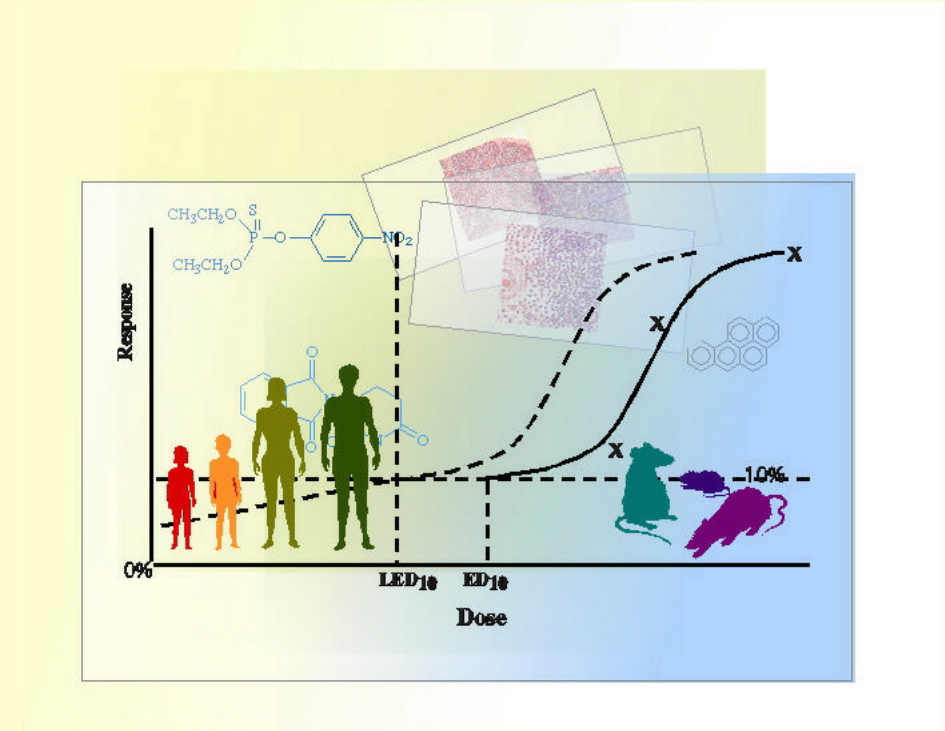
HUMAN HEALTH RISK ASSESSMENT

Ethion



U.S. Environmental Protection Agency
Office of Pesticide Programs
Health Effects Division (7509C)

Steven Knizner, Risk Assessor
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HUMAN HEALTH RISK ASSESSMENT

Ethion

Phase 4

Risk Assessment Team:

Lead Risk Assessor: Steven Knizner, Chemist
Dietary Risk: Dave Soderberg, Chemist
Occupational and Residential Exposure: Gary Bangs, Industrial Hygienist
Toxicology: Jess Rowland, Toxicologist

Management:

Senior Scientist: Steven Knizner, Chemist
Branch Chief: Jess Rowland, Toxicologist

Division Director: _____
Margaret J. Stasikowski, Date

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Executive Summary

The Health Effects Division (HED) has evaluated the ethion database. The toxicological database is adequate to support reregistration. Residue chemistry requirements are substantially complete pending submission of confirmatory data. However, additional data are required for certain occupational exposure scenarios.

Ethion (O,O,O',O'-tetraethyl S,S'-methylene bisphosphoro-dithioate) is an organophosphate insecticide. Ethion is labeled for use on citrus grown in Florida and Texas and as an eartag use for cattle. Ethion controls several varieties of mites and scales. Ethion is not registered for residential uses.

Applications can be made using ground equipment (airblast sprayers, high and low pressure handwands, and backpack sprayers). Except for the cattle eartag use, application types are restricted to spray/foliar treatments.

Hazard Identification

The toxicology database provides evidence that ethion, like other organophosphates, has anticholinesterase activity in all species tested including humans, dogs, rabbits, rats, and mice. Dogs appear to be the most sensitive species for inhibition of cholinesterase (ChE) activity.

Technical ethion is placed in Toxicity Category I for oral toxicity and in Category II for dermal and inhalation toxicity. For eye and dermal irritation, ethion is placed in Toxicity Category IV. Ethion is not a dermal sensitizer in guinea pigs and did not induce acute delayed neurotoxicity in hens.

Inhibition of plasma, erythrocyte, and/or brain cholinesterase (ChE) activity was seen following acute, subchronic, and chronic exposures by the oral, dermal and inhalation routes of exposures. Following subchronic oral administration, the No-Observable-Adverse-Effect-Level (NOAEL) for ChE inhibition was 0.05 mg/kg/day both in humans and dogs.

There was no indication of an increased susceptibility in rat or rabbit fetuses following prenatal exposure or in the offspring of rats after pre/postnatal exposure to ethion. Additionally, there was no evidence for requiring a developmental neurotoxicity study. Based on both the toxicity and exposure data, the FQPA Safety Factor (10X) for enhanced susceptibility of infants and children was removed.

Ethion has been classified as a "Group E" chemical; evidence of noncarcinogenicity in humans based on no evidence of carcinogenicity in two adequate animal (mice and rats) studies. Ethion was nonmutagenic both *in vivo* and *in vitro* when tested in a battery of mutagenicity assays. Confirmatory rat metabolism data for ethion are currently under review by the Agency.

Exposure and risk assessments were conducted for ethion as follows: acute and chronic dietary assessments to capture exposure estimates for the general public; and, dermal and inhalation exposure assessments to capture exposure estimates for occupational exposures. Residential exposure and risk assessments are not applicable since there are no registered residential uses at the present time.

Human Testing

On July 27, 1998 the Agency announced that it is deeply concerned about the conduct of pesticide health effects on human subjects and that it would be consulting with its independent Science Advisory Board (SAB) about the application of stringent ethical standards to any such studies. The Agency further stated that no human studies of this type have been used by EPA for any final decisions about acceptable levels of pesticide under the new food safety law. Agency officials have stated that no final agency regulatory determinations will be based on this kind of human study until the Agency has in place an approach for consideration of the ethical acceptability of any such study. At this time, the Agency has not yet received the response to its consultation with its scientific advisory committees and is continuing to work on its approach to these critical ethical questions.

During this period, EPA has continued to work through its risk assessment revisions and refinements for the organophosphates, including ethion, pursuant to the pilot process for public participation in risk assessment and risk management.

In previous assessments, reported in the Health Effects Division's Toxicity Endpoint Selection (TES) documents dated March 14, 1994 and October 10, 1995, the TES Committee based acute and chronic reference doses (RfD's), as well as occupational exposure and risk assessments, for ethion on a 21-day study conducted on human volunteers (MRID 00073157).

In light of the developing Agency policy on use of toxicology studies employing human subjects, and pending reassessment of this and other human studies for consideration of the ethical acceptability of such studies, HED has reconsidered the toxicology database for ethion and has for the acute dietary risk assessments, used a toxicology endpoint from an animal study and applied uncertainty factors informed by the existence of the human studies.

The standard uncertainty factor of 10 to account for interspecies extrapolation was reduced to 3. The intraspecies uncertainty factor of 10 was not reduced. Based on the NOAEL of 0.05 mg/kg/day established in an animal study, the acute dietary risk estimates do not exceed the Agency's level of concern for all populations, regardless of which interspecies factor was used (i.e., either 3 or 10).

All other risk assessments used only animal endpoints. OPP expects to reevaluate this acute dietary analysis pursuant to the Agency's decisions about how to consider the ethical acceptability of human studies and in light of the on-going efforts to develop peer-reviewed guidance for the scientific evaluation of any human studies that are determined to be ethically-appropriate for consideration in pesticide risk assessments.

Because EPA has not yet reached the stage of final Agency regulatory determination for ethion, we believe that the principle of transparency and the integrity of the pilot process for organophosphate reassessments justify the release of the refined risk assessment, although the issue of whether and how to consider the human studies on ethion toxicity has not yet been resolved. We believe this approach is also consistent with the Agency's stated positions on the consideration of human subject studies of pesticide toxicity.

For the acute dietary exposure risk assessment, the acute reference dose (RfD) of 0.0017 mg/kg/day was derived by the use of a NOAEL of 0.05 mg/kg/day and an uncertainty factor (UF) of 30 which includes 3X for interspecies extrapolation, as described above, and 10X for intraspecies variation. The NOAEL is based on plasma cholinesterase inhibition at 0.5 mg/kg/day (LOAEL) observed in a chronic toxicity study in dogs. Although the decrease in plasma cholinesterase inhibition was seen during Week 3 measurement, it was considered to be appropriate for acute dietary risk assessment since this was the earliest time point available for this risk assessment.

For the chronic dietary exposure risk assessment, the chronic RfD of 0.0005 mg/kg/day was derived by the use of a NOAEL of 0.05 mg/kg/day and an UF of 100

which includes 10X for interspecies extrapolation and 10X for intraspecies variation. The NOAEL is based on plasma, erythrocyte, and brain cholinesterase inhibition at 0.5 mg/kg/day (LOAEL) observed in a chronic toxicity study in dogs.

For the short- and intermediate-term dermal exposure risk assessments, a dermal NOAEL of 0.8 mg/kg/day was selected based on brain cholinesterase inhibition observed at 1.0 mg/kg/day following repeated dermal exposure to rabbits in two 21-day dermal toxicity studies.

For the inhalation exposure (any time period) risk assessments, an oral value (0.05 mg/kg/day) was selected with route-to-route extrapolation.

A Margin of Exposure (MOE, which is a ratio of a NOAEL to exposure) greater than 100 does not exceed HED's level of concern for all of the occupational exposure risk assessments.

Exposure and Risk Characterization

The main route of exposure to ethion for the general public (non-occupational exposures) is through food. Ethion has tolerances for citrus commodities and meat and milk. The meat and milk tolerances are required because of the feeding of citrus pulp to livestock and the eartag use. Dietary exposure is also possible as a result of residues potentially present in drinking water.

Both citrus metabolism and processing data indicate that the majority of ethion residues remain on the peel of citrus. Field trial data that were generated to support ethion tolerances in/on citrus measure residues in/on the whole fruit (peel and pulp). The USDA Pesticide Data Program (PDP) peels citrus fruits prior to analysis, reflecting consumer practices.

Dietary Exposure and Risk Characterization

Acute aggregate risk estimates do not exceed HED's level of concern. Acute aggregate risk estimates are derived using the combined acute dietary (food and water) exposure. Acute dietary food exposure has been highly refined using probabilistic techniques (Monte-Carlo), residue values derived from the USDA Pesticide Data Program (for citrus and milk), anticipated residues (for meat/milk), and incorporation of percent crop treated data. The detectable residues reported by PDP

were adjusted to reflect residues that could be potentially present in single serving sizes of commodities. This was necessary because PDP analyzes composite samples of commodities for residues rather than single servings for commodities.

Dietary risk estimates are based on the 99.9th percentile of exposure. Two probabilistic acute dietary risk analyses were conducted. In the first (and more conservative): PDP data for oranges were translated to all citrus (grapefruit, tangelos, tangerines, lemons, limes and kumquats); PDP data for orange juice were translated to all citrus juices; PDP data were used for milk; and acute anticipated residues were calculated for meat. Because no milk samples tested in the PDP program had detectable residues of ethion, one half the limit of detection was assumed. The second analysis was conducted exactly as the first except milk was considered to have negligible residues (i.e., no ethion was present). This is consistent with the policy concerning commodities having all non-detectable residues in monitoring programs, as presented at the Tolerance Reassessment Advisory Committee (TRAC meetings).

For the US Population, the percent of the acute RfD occupied for both of these scenarios is 8%. Similarly, for nursing infants less than one year old (the most highly exposed subpopulation) the percent of the acute RfD occupied is 28% and 25% respectively for the two scenarios.

Based on Environmental Fate and Effect Division (EFED) Tier 1 modeling for groundwater (SCI-GROW), the ethion estimated environmental concentrations (EECs) for groundwater is 0.05 ppb. Based on Tier 2 (PRZM-EXAMS) surface water modeling, the maximal (day 0) EEC for ethion in surface water is 25 ppb. This conservative modeling estimate does not exceed the 55 ppb drinking water level of comparison (DWLOC) for the US population. The calculated DWLOC for non-nursing infants is 12 ppb. EFED noted that the relatively high soil/water partitioning coefficient of ethion suggests that it will be effectively removed in most surface water source drinking water treatment utilities through primary settling and flocculation/coagulation followed by settling. Therefore, concentrations of ethion that may reach the consumer tap may be considerably less than those estimated by PRZM-EXAMS. HED thus concludes that acute aggregate exposure to ethion does not exceed our level of concern.

Chronic aggregate risk estimates do not exceed HED's level of concern. Chronic aggregate risk estimates are derived using the combined dietary (food and water) exposure. Chronic dietary food exposure has been highly refined using anticipated residues, processing data and percent crop treated data. Chronic anticipated residues for citrus commodities were calculated using either PDP or FDA monitoring data. Partially refined (Tier 2, PRZM-EXAMS) EECs have been calculated for surface water. Tier 1 modeling has been conducted for groundwater (SCI-GROW).

Based on toxicological endpoints from the animal toxicity studies, chronic dietary exposure from food alone does not exceed HED's level of concern. The percent of the chronic RfD occupied from chronic food exposure alone ranges from 7% for the US Population to 21% for children 1-6 years old. The chronic DWLOC for the US

population is 16 ppb and for children it is 4 ppb. EFED recommended that 1 ppb be considered the chronic exposure level for ethion residues in surface water and 0.05 ppb for groundwater. This value is below the calculated DWLOCs. HED thus concludes that chronic aggregate exposure to ethion does not exceed our level of concern.

Because there are no registered uses for ethion that could result in residential exposures, short- and intermediate-term aggregate risk assessments are not required.

Occupational Exposure and Risk Characterization

Mixing/Loading/Applying

The exposure data for estimating the risk to mixer/loaders (airblast, aerial, and high pressure handwand) are based on high quality data for baseline, additional protection equipment and engineering controls. The applicator risk estimate for airblast applications is based on high quality exposure data for the three levels of protection. The risk estimates for the remainder of the scenarios (backpack, low pressure handwand and high pressure handwand) are based on low quality data and HED has low confidence in the exposure and risk estimates.

For ethion, an MOE of greater than 100 does not exceed HED's level of concern for occupational exposures. The MOEs with baseline attire are less than 100 for every exposure scenario where data are available. No data are available for backpack sprayers at baseline attire. Adding engineering controls to baseline attire, the MOEs for mixing and loading airblast and hand wand application no longer exceeded HED's level of concern (MOEs of 130 and 110 respectively). However, airblast application continued to be of concern (MOE of 50).

No feasible engineering controls are available for high-pressure handwand application, low-pressure handwand mixing/loading/applying, or backpack sprayer mixing/loading/applying, so those exposure scenarios remain a concern.

Post-Application Exposure

The transfer coefficient (Tc) for this exposure assessment was estimated based on the reasonable worst-case task of harvesting citrus. Dislodgeable Foliar Residue (DFR) data were available for ethion and these data were adjusted for the current application rate (2.5 lb ai/acre) since the study was conducted at a slightly higher rate. DFR data from the citrus studies were chosen by EPA as the best available DFR data but it should be noted that the study used to generate these data was deemed unacceptable. The MOE, based on the toxicity endpoint for the ethion parent only, for post-application exposures reaches 100 for total exposure (ethion plus oxon) at day 8 following application. However, the acute toxicity of the ethion-oxon(s) may be 2-3 times that of the parent. Considering the degradation rate of ethion to the oxon(s) and the toxicity of the oxon(s) as compared to the parent a re-entry interval (REI) of 8 days may result in a risk to the worker that exceeds HED's level of concern. Taking into account the incidents in California, and until adequate toxicity data are available to appropriately assess the risk to workers from the oxon(s), HED recommends that an REI of not less than 8 days be imposed. The adequacy of the REI will be reevaluated upon receipt and review of the data requested to determine the toxicity of the ethion oxon(s).

I. Hazard Assessment

A. Toxicity Assessment

The toxicological database for the parent compound, ethion, is complete and will support reregistration. In order to more accurately assess the toxicity of oxon products, the Agency is requiring acute dermal toxicity studies (Guideline 81-2) with the monooxon and dioxon metabolites of ethion. Lack of these acute studies at the present time does not impact occupational risk assessments conducted with the parent compound.

1. Acute Toxicity

The acute toxicity data on technical ethion are summarized in Table 1.

Table 1: Acute Toxicity of Ethion Technical

Study	Results	Category	MRID#
Acute Oral LD_{50} (rat)	191 mg/kg (M) 21 mg/kg (F)	I	00157590
Acute Dermal LD_{50} (rat)	838 mg/kg	II	00157590
Acute Inhalation LC_{50} (rat)	2.31 mg/L (M) 0.45 mg/L (F)	II	00163159
Primary Eye Irritation (rabbit)	slight redness	IV	00157590
Primary Dermal Irritation (rabbit)	slight erythema	IV	00157590
Dermal Sensitization (guinea pig)	non sensitizer	N.A.	00141205
Acute Neurotoxicity (hen)	no evidence of acute delayed neurotoxicity	N.A.	00158376

2. Subchronic Toxicity

In a 90-day oral toxicity study in dogs, ethion was administered in the diet to beagle dogs at concentrations of 0, 0.5, 2.5, 25, or 300 ppm (0.0125 to 7.5 mg/kg/day). The systemic toxicity NOAEL was 25 ppm (0.71 mg/kg /day) and the LOAEL was 300 ppm (6.9 mg/kg/day in males, 8.25 mg/kg/day in females), based on reductions in body weight gain and food consumption and on clinical signs of toxicity--ataxia, emesis, miosis and tremors. Ethion inhibited brain cholinesterase activity in 25 and 300 ppm treated dogs (both sexes), erythrocyte cholinesterase activity in 300 ppm treated dogs (both sexes), and plasma cholinesterase activity in 2.5, 25.0, and 300 ppm treated dogs (both sexes). The NOAEL for

cholinesterase (ChE) inhibition was 0.5 ppm (0.01 mg/kg/day). The LOAEL for inhibition of plasma was 2.5 ppm (<14%M/<15%F in week 5; M<15% week 13), brain was 25 ppm (<23%M), and erythrocyte ChE is 300 ppm (<94%M/<96%F in week 5; <94%M/<93%F in week 13) (MRID# 40773301).

The requirement for a subchronic oral toxicity study in rodents is satisfied by a 2-year chronic/carcinogenicity feeding study in rats (MRID# 00148991, see below, 4. Carcinogenicity, for details of study).

Two 21-day dermal toxicity studies were conducted with ethion in rabbits. In one study, the doses were 0, 1, 3, 25, or 250 mg/kg/day. Erythema and desquamation at the application sites occurred in both sexes at doses of 25 mg/kg/day (systemic LOAEL) or more, and inhibition of ChE activity in the brain occurred at 1 mg/kg/day (<18%M). Plasma and red cell inhibition of cholinesterase was statistically significant at the 25 mg/kg/day dose (plasma 37%F, RBC <32%M) and the 250 mg/kg/day dose level (plasma <47%M/<60%F; RBC <49%MF). The NOAELs for systemic toxicity and ChE inhibition were 3 mg/kg/day and less than 1 mg/kg/day (lowest dose tested), respectively (MRID 00155498). A second study with New Zealand white rabbits included lower doses of ethion at 0, 0.1, 0.25, 0.5, 0.8, 1, 3, or 25 mg/kg/day. Inhibition of brain ChE activity occurred at 1 mg/kg/day (<16%combined M/F) or more (MRID 00155499). When the results of the two dermal studies were combined, the NOAEL for ChE inhibition was established at 0.8 mg/kg/day.

3. Chronic Toxicity

In a dog chronic toxicity study (MRID 41188401), beagle dogs were fed diets containing ethion at 0, 0.5, 1, 2, 20, or 100 ppm (0, 0.011, 0.026, 0.049, 0.52 or 2.53 mg/kg/day to males and at 0, 0.011, 0.028, 0.053, 0.53 or 2.56 mg/kg/day to females) for 52 weeks. There was a dose-related decrease in plasma cholinesterase activity in males (16-20%) and females (7-17 %) at 0.049 mg/kg/day and throughout treatment (50 to 75% in both sexes) at the higher doses. The toxicology reviewer, established the 0.049 mg/kg/day as the LOAEL based on the plasma cholinesterase inhibition; the NOAEL was established at 0.026 mg/kg/day. Erythrocyte ChE activity was decreased at higher doses (20 ppm in females). Both erythrocyte and brain ChE activities were decreased at 100 ppm. However, closer examination of the data showed that the decrease in plasma cholinesterase activity was statistically significant at 0.049 mg/kg/day only at week 3 (the earliest time point of measurement)

and not at subsequent time points. Statistically significant inhibition of plasma cholinesterase activity was seen at the higher doses at all measurement periods.

NOTE: The toxicology reviewer selected the 0.049 mg/kg/day as the LOAEL in the 1-year dogs study and the 0.06 mg/kg/day as the LOAEL in the 90-day dog study. Upon further consideration, however, HED changed these values (i.e., 0.049 mg/kg/day and LOAEL of 0.06 mg/kg/day) to be NOAELs for risk assessment purposes only (see decision logic presented below in Acute Dietary Endpoint Selection section). These changes are NOT reflected in the Data Evaluation Records of these studies.

4. Carcinogenicity

Ethion is classified as a "Group E" Chemical (Not a human carcinogen) based on lack of evidence of carcinogenicity in male and female mice or male and female rats.

In a chronic/carcinogenicity feeding study, male and female Sprague-Dawley rats were fed diets containing 0, 2, 4, or 40 ppm ethion (0.1 to 2.0 mg/kg/day) for 24 months. The only effects observed were reductions in serum ChE activity at 40 ppm, which occurred in females at 6, 12 and 18 months and in males at 12 and 18 months. The NOAEL for ChE inhibition was 4 ppm (0.2 mg/kg/day) and the systemic toxicity NOAEL exceeded 40 ppm (HDT). No carcinogenic effects were observed (MRID# 00148991).

In a carcinogenicity feeding study, male and female CF1 mice were fed diets containing 0, 0.75, 1.5, or 8 ppm ethion (0.11 to 1.2 mg/kg/day) for 2 years. The NOAEL was 1.5 ppm (0.225 mg/kg/day) and the LOAEL was 8 ppm for both sexes, based on decreased plasma ChE activity. No carcinogenic effects were observed; tumor incidence was comparable between treated and control animals (MRID# 00148989).

5. Developmental Toxicity

In a rat developmental toxicity study, Charles River rats were gavaged with 0, 0.2, 0.6 or 2.5 mg/kg/day ethion on gestation days 6-15. Both the maternal and developmental toxicity NOAELs were 0.6 mg/kg/day. Both the maternal and developmental toxicity LOAELs were 2.5 mg/kg/day, based on signs of hyperactivity in the parents and on delayed ossification of pubes in the fetuses (MRID# 00131852).

In a rabbit developmental toxicity study, New Zealand white rabbits were administered 0, 0.6, 2.4 or 9.6 mg/kg/day ethion by gavage on gestation days 6-18. The NOAEL for maternal toxicity was 2.4 mg/kg/day and the LOAEL was 9.6 mg/kg/day due to weight loss, reduced food

consumption, and orange colored urine. The NOAEL for developmental toxicity was the highest dose tested (MRID# 00131853).

6. Reproductive Toxicity

In a three-generation study in which ethion was fed to Charles River rats at concentrations of 0, 2, 4 or 25 ppm, the reproductive NOAEL was 25 ppm (1.25 mg/kg/day), the highest dose tested. The systemic toxicity NOAEL was 25 ppm in male rats and the LOAEL was 4 ppm (0.2 mg/kg/day) in F_1 and F_2 female rats due to a decrease in serum ChE activity at the highest concentration (MRID# 00148990).

7. Mutagenicity

Results of mutagenicity studies indicate that ethion does not appear to be mutagenic. The results of these studies are summarized in Table 2.

Table 2: Mutagenicity Studies with Ethion

Study Type	Results
Gene Mutation/Ames	Negative, w/wo metabolic activation, at ≤10000 ug/plate (MRID# 00144351) or at ≤20000 ug/plate (MRID# 00096523).
Structural Chromosome Aberration (in-vivo cytogenic test/rats	Negative in male rats treated with 4.7, 14, 47, or 140 mg/kg/day (MRID# 00142546).
Unscheduled DNA Synthesis in-vitro (rat hepatocytes)	Negative at levels of 0.625, 1.25, 2.5, 5, or 10 ng/ml. (MRID# 00142545)
Recombinant/Conversion Assay in S. cerevisiae	Negative, w/wo metabolic activation at ≤10% v/v (i.e. 10000 ppm) (MRID# 00096522)

8. Metabolism

Metabolism data were submitted, but are still in review. These confirmatory metabolism studies are required for the continued registration of ethion.

9. Neurotoxicity

An acute delayed neurotoxicity study (1982) was conducted using white female leghorn hens. The hens were administered a single oral dose of 1900 mg/kg ethion (92%). Axonal swelling below the spinal cord was observed in 19/34 hens. The LD_{75} is 1901 mg/kg. This is considered a positive study for neurotoxicity (MRID 248175). An acute delayed neurotoxicity study (1986) was conducted on female domestic hens. The hens were dosed at 2792 mg/kg (2219-3831 mg/kg) followed by a second dose 21 days later. Neither dose produced clinical nor histopathological signs of neurotoxicity. The acute delayed neurotoxicity LD_{50} is 2792 mg/kg (MRID 00158376). Neither study assessed for the potential of ethion to inhibit neurotoxic esterase (NTE) in hens.

In an acute neurotoxicity study (MRID #43151301), rats (10 animals/sex/group) received ethion (92.2% a.i.) by gavage (in corn oil). Doses were 10, 20, and 40 mg/kg for females, 20, 40, and 80 mg/kg for males. Clinical observations were recorded daily, body weight was recorded weekly, and animals were evaluated using a functional observation battery (FOB) and motor activity testing at one week prior to test compound administration, at the time of peak effect (approximately 5 hours after compound administration), and at 7 and 14 days after compound administration. Cholinesterase inhibition was not evaluated. At study termination on day 14, 5 rats/sex/group were perfused with glutaraldehyde/paraformaldhyde, and histopathological evaluation of peripheral and central nervous system tissue was performed on 5 animals/sex of the control and high dose group. No treatment-related effects were seen at the lowest dose level for either sex (10 mg/kg for females, 20 mg/kg for males). At the mid-dose level (20 mg/kg for females, 40 mg/kg for males), clinical signs were observed in both sexes (diarrhea in males only, staggered gait in both sexes, and tremors in females only). FOB effects were also seen in both sexes at this dose level (day 0 only, most notably tremors and gait impairments (including staggered gait) in both sexes, decreased hind limb grip strength in females only). No change in motor activity was seen at this dose level. At the high dose level (40 mg/kg for females, 80 mg/kg for males), one treated female died. In surviving animals, increased incidence of the clinical signs noted at the mid-dose level were observed, as well as additional clinical signs not seen at lower dose level (most notably head swaying and oral discharge in males, abdominal gripping, exophthalmos, lacrimation, oral discharge, and splayed hindlimbs in females). In addition to an increased incidence of FOB effects noted at mid-dose, FOB findings seen at high dose (seen on day 0 only) included stereotyped

behavior, ataxia, miosis, and staggered gait in both sexes; females also had increased incidence of limpness on handling, exophthalmus, lacrimation, salivation, unthrifty appearance, absent auditory response, abnormal righting reflex, decreased forelimb and hindlimb grip strength and increased tail flick latency. No change in motor activity was seen in males, but decreased motor activity was seen in females at day 0 and day 7. There were no histopathological findings related to treatment. The LOEL was 20 mg/kg for females, 40 mg/kg for males, based on clinical signs and FOB effects (staggered gait, tremors, decreased grip strength); the NOEL for neurotoxicity was 10 mg/kg for females, 20 mg/kg for males. The study is classified as acceptable and satisfies guideline requirements (Section 81-8) for an acute neurotoxicity study in rats.

In a subchronic neurotoxicity study (MRID #43450101), rats (10 animals/sex/group) received ethion (92.2% a.i.) in the food at 0, 100, 500, or 800 ppm (0, 6.2, 31.3 or 51.7 mg/kg/day) for males or 0, 30, 100, or 300 ppm (0, 2.2, 7.3, 22.5 mg/kg/day) for females. Clinical observations were recorded daily, body weight and food consumption were recorded weekly. Functional observation battery (FOB) and motor activity were evaluated at pre-test, 4, 8, and 13 weeks. At completion of behavioral testing, five animals per sex per group were perfused; peripheral and central nervous system tissues were evaluated histopathologically for control and high dose groups only. Cholinesterase inhibition was not measured. No treatment-related effects were seen at the low dose in either sex (2.2 mg/kg/day for females, 6.2 mg/kg/day for males), or at mid dose in females (7.3 mg/kg/day). For mid dose males (31.3 mg/kg/day), the only treatment-related effect seen was a lower body weight (decreased by approximately 6-8% at varying time points). At the high dose level (22.5 mg/kg/day for females, 51.7 mg/kg/day for males), one treated female died. In surviving animals, there was increased incidence of clinical signs (tremors and staggered gait for males and females; additional signs seen only in females included exophthalmus, decreased feces, splayed hindlimbs, and unthriftiness). Effects were also noted in both sexes on the FOB, included those observed as clinical signs (both sexes), as well as abnormal posture, splayed hindlimbs, and decreased grip strength (in females only). Incidence of clinical signs and FOB effects increased at later time points, such that the highest incidence was at week 13. Motor activity was unchanged in males but decreased in females, at week 13 only. In addition, an increase in axonal degeneration (most notably in sciatic nerve of males), was found at this dose level. A NOAEL/LOAEL has not been established since the need for additional histopathological examination is under review at the present time. The lack of a NOAEL/LOAEL in this study does not have any impact on risk

assessment since the doses used for risk assessments are lower than the lowest dose tested in this study. This study is classified as "conditionally" acceptable pending final determination for the need for additional histopathology data.

10. Human Special Toxicity Study

From a human special toxicity study, the dose of 0.05 mg/kg/day was selected as the NOAEL based on clinical signs of cholinesterase inhibition observed at the lowest dose in six male human volunteers given gelatin capsules containing ethion at doses of 0.05, 0.075, 0.10 or 0.15 mg/kg/day for 21 days (MRID No. 00073157). In this study, there were no effects on erythrocyte cholinesterase activity. No consistent effects were seen on plasma cholinesterase activity. Statistically significant decreases (15% to 31%) in plasma cholinesterase activity were observed at doses of 0.075 mg/kg/day and higher. Cholinergic signs indicative of cholinesterase inhibition was seen in one subject given 0.05 mg/kg/day toward the end of the dosing period (days 19-21) and in the other subject on the first day of the next higher dose (0.075 mg/kg/day). The first subject reported headache and blurred vision on days 19 to 21 and light headedness and dizziness on the following day. The second subject reported partial blindness and light headedness twice on the first day of receiving 0.075 mg/kg/day. These results indicated that the occurrence of cholinergic signs in 2 of 6 subjects and taken together, can be interpreted as a reflection of a cumulative effect of ethion at 0.05 mg/kg/day (i.e., a NOAEL was not achieved for clinical signs at any dose).

11. Dermal Absorption

In a published study [Toxicol. Appl. Pharmacol. 28: 126-132 (1974); MRID #43736616], C^{14}-labeled ethion was applied to the skin of the ventral forearm of six male humans in a 0.25% acetone solution at a rate 4 µg/cm^2. The acetone solution was pipetted onto the area marked by a ring and evaporated by gentle blowing during application: the solvent was on the skin for only a few seconds. The skin sites were left unprotected and the subjects were asked not to wash the area for 24 hours. Urine was collected for 5 days for measurement of excreted radioactivity. To correct for incomplete urinary recovery, prior to the dermal study the volunteers were dosed intravenously (iv) with a tracer dose of the radiolabeled material in the weight range of the cutaneous exposure. Urine was also collected for 5 days for measurement of radioactivity. Excretion of radioactivity in urine after dermal dosing amounted, after correction with the iv data, to 3.3% ± 1.1% of the dose.

The results of this study indicated a 3.3% dermal absorption factor.

In the previous risk assessment, a dermal absorption factor of 3.3% was used since an oral value (based on the human study) was selected for dermal exposure scenarios. For the current risk assessment, however, a

dermal absorption factor is not required since a dermal NOAEL (from a 21-day rabbit dermal toxicity study; MRID 00155498) is used for occupational dermal exposure risk assessments.

12. Other Toxicological Considerations

As noted in the Occupational Exposure Section, ethion and its oxon oxidation product(s) have been detected in the dislodgeable residues of citrus crops in amounts ranging from about 16.3% of the residue at three days after treatment up to about 26.9% of the residue at seven days after treatment. Thus, there is some concern for the impact that exposures to these oxidation products of ethion may have on MOEs for field workers.

At this time the Agency does not have toxicity data on the oxon products (mono- or di-) of ethion, however, it is generally considered that most oxon metabolites (with a P=O group) of a phosphothionate pesticide have a higher mammalian acute toxicity than the unoxidized (with a P=S group) parent (Maxwell and Lenz, 1992; Ecobichon, 1991).

As summarized below for two related phosphorodithioates:

- ❏ In female rats, the oxon of disulfoton (acute oral LD_{50} = 1.17 mg/kg) is 2.2-1.6 times more acutely toxic orally than the parent disulfoton (acute oral LD_{50} = 2.6-1.9 mg/kg) [Kaemmerer and Buntenkotter (1976); Crawford, C.R. and Anderson, R.H. (1974)].

- ❏ In the mouse, the oxon of carbophenothion (PTMD, acute oral LD_{50} = 165 mg/kg), is 1.3 times more acutely toxic orally than the parent carbophenothion (LD_{50} = 217 mg/kg) [Eto (1974)].

Additionally, for other thionates no longer possessing the above phosphorodithioate functionality, the oxon has also been found to have equal or greater toxicity than the parent thionate:

- ❏ In rats, the oxon of the phosphonothionate fonofos (acute oral LD_{50} = 2.7 mg/kg) is 6.5 times more acutely toxic than parent fonofos (acute oral LD_{50} = 16 mg/kg) [Eto (1974)].

- ❏ In rats, the di-oxon of the phosphorothionate sulfotepp (Tepp, acute oral LD_{50} = 1.2-2.0 mg/kg) is 2.5-4.1 times more acutely toxic than the parent sulfotepp (acute oral LD_{50} = 5 mg/kg) [Eto (1974)]. It is noted, additionally, that the mono-oxon of sulfotepp, with a rat

LD_{50} of 0.5 mg/kg [Eto (1974)] appears to be 10 times more acutely toxic orally than its parent sulfotepp.

- In rats, the oxon of the phosphorothionate parathion (paraoxon, acute oral LD_{50} = 3-4 mg/kg) is 1-2.5 times more acutely toxic than the parent paraoxon (acute oral LD_{50} 4-7 mg/kg) [Kaemmerer and Buntenkotter, (1976), Ahmed et al. (1960)].

The above cited toxicity data for phosphorodithioates suggest that the ethion oxon(s) could be more acutely toxic as the thiono parent by the oral route. And by analogy with the tepp/sulfotepp pair (where the case of an oxon/dioxon pair is possible) could be up to 10 times as acutely toxic.

Occupational exposure to the oxon(s) of ethion may occur. Although the toxicity data for phophorodithioates suggests the ethion oxon(s) could be at least 1.3 to 2.2 times as acutely toxic as the thiono parent by the oral route, at this time, the hazard associated with the ethion oxon(s) is not quantifiable.

To more accurately assess the toxicity and risk associated with ethion and the ethion oxon(s) the Agency is requiring the following three studies: guideline 81-2 acute dermal LD_{50} toxicity in rats conducted with the monooxon, dioxon, and parent ethion. *These studies should include cholinesterase measurements.* The Agency will determine the need for additional studies after review and evaluation of the results of the acute dermal studies with the oxon products along with the toxicology database (with special emphasis on dermal toxicity studies) for the parent compound.

B. Dose Response Assessment

1. Special Sensitivity to Infants and Children

On August 8, 1998, HED FQPA Safety Factor Committee evaluated both the hazard and exposure data and recommended that the 10X FQPA Safety Factor for ethion could be removed based on the following weight-of-evidence:

(a) In prenatal developmental toxicity studies, there was no evidence of enhanced susceptibility in fetuses as compared to maternal animals following *in utero* exposure in rats and rabbits.

(b) In the pre/post natal two-generation reproduction study in rats, there was no evidence of enhanced susceptibility in pup when compared to adults.

(c) There was no evidence of abnormalities in the development of the fetal nervous system in the pre/post natal studies. Neither brain weight nor histopathology (nonperfused) of the nervous system was affected in the subchronic and chronic toxicity studies in rats and dogs.

(d) There was no evidence for requiring a developmental neurotoxicity study in rats.

(e) The toxicology database is complete to assess susceptibility to infants and children.

(f) Adequate actual data, surrogate data, and/or modeling outputs are available to satisfactorily assess dietary (food) exposure and to provide a screening level drinking water exposure assessment.

2. Toxicology Endpoint Selection

In previous assessments, the Health Effects Division's Toxicology Endpoints Selection Committee (TESC) selected doses and endpoints from the 21-day study conducted in human volunteers (MRID 73157). for acute and chronic dietary as well as occupational exposure risk assessments (TES Documents dated 3/14/94, 10/10/95).

On July 27, 1998 the Agency announced that it is deeply concerned about the conduct of pesticide health effects on human

subjects and that it would be consulting with its independent Science Advisory Board (SAB) about the application of stringent ethical standards to any such studies. The Agency further stated that no human studies of this type have been used by EPA for any final decisions about acceptable levels of pesticide under the new food safety law. Agency officials have stated that no final agency regulatory determinations will be based on this kind of human study until the Agency has in place an approach for consideration of the ethical acceptability of any such study. At this time, the Agency has not yet received the response to its consultation with its scientific advisory committees and is continuing to work on its approach to these critical ethical questions.

During this period, EPA has continued to work through its risk assessment revisions and refinements for the organophosphates, including ethion, pursuant to the pilot process for public participation in risk assessment and risk management.

In light of the developing Agency policy on use of toxicology studies employing human subjects, and pending reassessment of this and other human studies for consideration of the ethical acceptability of such studies, HED has reconsidered the toxicology database for ethion and has for the acute dietary risk assessments, used a toxicology endpoint from an animal study and applied uncertainty factors informed by the existence of the human studies.

The standard uncertainty factor of 10 to account for interspecies extrapolation was reduced to 3. The intraspecies uncertainty factor of 10 was not reduced.

All other risk assessments used only animal endpoints. OPP expects to reevaluate this acute dietary analysis pursuant to the Agency's decisions about how to consider the ethical acceptability of human studies and in light of the on-going efforts to develop peer-reviewed guidance for the scientific evaluation of any human studies that are determined to be ethically-appropriate for consideration in pesticide risk assessments.

Consequently, the doses and toxicology endpoints were selected through this process, and are potentially subject to further revision when policy development concerning human studies is completed and the relevant human studies have been reassessed. Presented below are the doses and toxicology endpoints selected by HED's Hazard Identification Assessment Review Committee (HIARC) based on animal toxicity studies

with ethion.

a. Acute Dietary (Acute Reference Dose)

In a chronic toxicity study (MRID No. 41188401), beagle dogs were fed diets containing ethion at 0, 0.011, 0.026, 0.049, 0.52 or 2.53 mg/kg/day to males and at 0,0.011, 0.028, 0.053, 0.53 or 2.56 mg/kg/day to females for 52 weeks. There was a dose-related decrease in plasma cholinesterase activity in males (16-20%) and females (7-17 %) at 0.049 mg/kg/day and throughout treatment (50 to 75% in both sexes) at the higher doses. The NOAEL was established at 0.026 mg/kg/day based on plasma cholinesterase inhibition at 0.049 mg/kg/day.

However, closer examination of the data showed that the decrease in plasma cholinesterase activity was statistically significant at 0.049 mg/kg/day only at week 3 (the earliest time point of measurement) and not at subsequent time points. Statistically significant inhibition of plasma cholinesterase activity was seen at the higher doses at all measurement periods. Additionally inhibition of erythrocyte and brain cholinesterase activity was seen in both sexes of dogs at higher doses. HED concludes that the dose of 0.049 mg/kg/day can be considered as the NOAEL since the decrease in plasma cholinesterase activity was seen only at one interval (i.e., during week 3 measurement), is of minimal magnitude ($\leq$ 20%). Since this is the shortest time point available it therefore is appropriate for acute dietary risk assessment. In addition, this dose as a NOAEL is supported by the results of the 90-day study in dogs (MRID No. 40773301), which also demonstrated a NOAEL of 0.06 mg/kg/day for inhibition of plasma cholinesterase activity at weeks 5, 9 and 13 and inhibition of brain cholinesterase activity at week 13 of study.

An **acute RfD** was derived based on an a NOAEL of 0.05 mg/kg/day and an UF of 30 to account for interspecies extrapolation (3X), intraspecies variation (10X) and the FQPA Safety Factor (1x).

$$\textbf{Acute RfD} = \frac{0.05 \text{ mg/kg/day (NOAEL)}}{30 \text{ (UF)}} = \textbf{0.0017 mg/kg}$$

Conventionally, when a NOAEL from an animal study is selected, an UF of 100 (10X for interspecies extrapolation and 10X for intraspecies variation) is used. However, the HIARC

determined that an UF of 30 is adequate for acute risk assessment. The HIARC concluded that the human study (Palzzollo, 1970) is useful as supplemental data. The HIARC determined that the interspecies factor could be reduced since a clear NOAEL for an acute (single) exposure was established in the dog study for the principal effect (i.e., plasma cholinesterase inhibition) and the degree of plasma cholinesterase inhibition was similar in dogs and humans after the same period (21-days) of exposure. At the Day 21 measurement, plasma cholinesterase was 90.8% of pretreatment in humans and 83% of pretest in dogs at the same dose (0.05 mg/kg/day). Based on these comparative data, it was presumed (i.e., extrapolated from day 21 to day 1) that there would have been comparable effects after single (one day) exposure in humans.

Although these data indicated that humans are unlikely to be more sensitive to acute exposures to ethion than other species, the HIARC determined that a 3X interspecies extrapolation factor is required. While the human study did provide insight as to when the cholinesterase inhibition in humans is likely to occur, it was not rigorous enough for endpoint selection. There was concern that brain cholinesterase inhibition (not measurable in humans) could occur at doses causing plasma cholinesterase inhibition since this has been demonstrated in other species. In addition, the study included only 6 male subjects.

b. Chronic Dietary (Chronic Reference Dose)

A NOAEL of 0.049 mg/kg/day based on inhibition of plasma, erythrocyte and brain cholinesterase activity at 0.5 mg/kg/day in both sexes of dogs was selected for deriving the chronic RfD (MRID No. 41188401; discussed above, see Acute Dietary).

The **chronic RfD** was derived based on a NOAEL of 0.05 mg/kg/day and an UF of 100 to account for interspecies extrapolation (10X), intraspecies variation 10X), and the FQPA Safety Factor (1X).

$$\textbf{Chronic RfD} = \frac{0.05 \text{ mg/kg/day (NOAEL)}}{100 \text{ (UF)}} = \textbf{0.0005 mg/kg}$$

The HIARC concluded that the 10X interspecies extrapolation factor cannot be modified/altered. The study in humans (Palzzollo, 1970) is useful only as supplemental data. Although this study provided supportive scientific data, it is not adequate for use in chronic risk assessment because the treatment regimen (21-days) is not adequate to characterize lifetime exposure. Unlike for acute exposure, relative sensitivity of humans following chronic exposure could not be ascertained due to the lack of data following longer exposure durations (i.e., 21 day exposure in humans and 1-year exposure in dogs). There is concern for the occurrence of brain cholinesterase inhibition (not measurable in humans) at the same levels as plasma cholinesterase inhibition in animals.

c. Carcinogenicity Classification

Based on the lack of evidence of carcinogenicity in mice and rats, ethion is classified as a Group E Chemical; evidence of noncarcinogenicity for humans.

d. Occupational Exposure

For occupational dermal exposure risk assessments, the HIARC selected the dose and endpoint from the combined results of two 21-day dermal toxicity studies in rabbits. Residential exposure risk assessment is not required since there are no residential uses or other uses that could result in residential exposures at the present time.

In one study (MRID No. 00155498), when tested at 0, 1.0, 3.0, 25, or 250 mg/kg/day, inhibition of brain cholinesterase activity occurred at all levels including the lowest dose tested (1 mg/kg/day). Since a NOAEL was not established, a second study in rabbits (MRID 00155499) tested lower doses at 0, 0.1, 0.25, 0.5, 0.8, 1.0, 3.0, or 25 mg/kg/day). Inhibition of brain ChE activity occurred at 1 mg/kg/day or more. Based on the results of the two studies, for brain cholinesterase inhibition, the NOAEL was 0.8 mg/kg/day and the LOAEL was 1 mg/kg/day.

(i). Short-Term Dermal

The dermal NOAEL of 0.8 mg/kg/day was selected for this exposure scenario; a MOE greater than 100 does not exceed HED's level of concern for this risk assessment.

(ii). Intermediate-Term Dermal

The dermal NOAEL of 0.8 mg/kg/day was also selected for this exposure scenario since data from oral and dermal studies indicate ChE inhibition reaches a peak within a few weeks and further depression does not occur following longer exposure periods. A MOE greater than 100 does not exceed HED's level of concern for this risk assessment.

(iii). Long-Term Dermal

The dermal NOAEL of 0.8 mg/kg/day was also selected for this exposure scenario for reasons stated above under intermediate-term. A MOE greater than 100 does not exceed HED's level of concern for this risk assessment.

(iv). Inhalation Exposure (Any Time Period)

Only an acute inhalation toxicity study was available. Therefore, the oral NOAEL (from the 1-year dog study) was selected for inhalation exposure risk assessments; the route-to-route extrapolation was used as follows:

Step I. Convert the inhalation exposure component (i.e., µg a.i/day) using a 100% absorption rate (default value) and an application rate to an **equivalent oral dose** (mg/kg/day)

Step II Compare the oral equivalent dose to the oral NOAEL of 0.05 mg/kg/day to calculate the MOE's. A MOE greater than 100 does not exceed HED's level of concern for for this risk assessment.

Note: Inhalation and dermal exposures should not be combined since a dermal NOAEL was selected for dermal risk assessments and an oral NOAEL was selected for inhalation risk assessments. However, as shown below, the MOEs, can be combined since a common toxicological endpoint (i.e., cholinesterase inhibition) was observed following oral and dermal routes of exposure.

$$\frac{1}{\frac{1}{MOE_{Oral}} + \frac{1}{MOE_{Dermal}} + \frac{1}{MOE_{Inhalation\ (oral\ equivalent)}}}$$

Table 3. Summary of Toxicology Endpoints Selected Based on Animal Toxicity Studies

Exposure Period	Use of an Animal Study
Acute Dietary	NOAEL =0.05 mg/kg UF = 30 **Acute RfD = 0.0017 mg/kg**
Chronic Dietary	NOAEL =0.05 mg/kg UF =100 **Chronic RfD =0.0005 mg/kg/day**
Dermal absorption	Not Required - Dermal NOAEL used
Short-Term Dermal	Dermal NOAEL = 0.8 mg/kg/day MOE greater than 100 does not exceed HED's level of concern
Intermediate-Term Dermal	Dermal NOAEL = 0.8 mg/kg/day MOE greater than 100 does not exceed HED's level of concern
Long-Term Dermal	Dermal NOAEL = 0.8 mg/kg/day MOE greater than 100 does not exceed HED's level of concern
Inhalation Exposure (Any Time period)	Oral NOAEL = 0.05 mg/kg/day Inhalation absorption 100% MOE greater than 100 does not exceed HED's level of concern

II. Exposure Assessment

A. Dietary (food/drinking H_20) Exposure & Risk Characterization

1. Dietary Exposure - Food Sources

a. Plant Metabolism

The qualitative nature of the residue in citrus is adequately understood based on an acceptable orange metabolism study. Based on the data, residues are not translocated from treated leaves or fruits. Residues in oranges are found primarily in the peel (>99% of TRR in the mature fruit), and ethion *per se* is the major (ca. 70-80%) terminal residue. Ethion monooxon and ethion dioxon are minor metabolites accounting for <1% of the terminal residue on the day of treatment and 9% and 3% respectively, 90 days post-treatment (MRID#s 00155869, 00155870).

b. Animal Metabolism

Ruminant - The qualitative nature of the residue in ruminants is adequately understood based on an adequate goat metabolism study. In the ruminant metabolism study, goats were dosed with [^{14}C]ethoxy-labeled ethion at 25 ppm in the diet (approximately 5x the maximum theoretical dietary burden). In milk, the majority of radioactivity (>88%) is incorporated into natural constituents (fatty acids, proteins, and sugars). Ethion and O,O-diethyl phosphate (EOOP) are minor metabolites in milk accounting for 2.8 and 0.7% of the terminal residue, respectively. In fat, the majority of the residue (>70%) is incorporated into fatty acids, but ethion accounts for approximately 18% of the terminal residue. In kidney, the predominant metabolite is O,O-diethyl phosphate (EOOP; 51.5% TRR). The sodium salt of O,O-diethyl phosphoro-thionate (ESOP) and O,O-diethylphosphorodithioic acid (ESSP) are minor metabolites in kidney accounting for 7.0% and 3.3% of the terminal residue, respectively. Only trace levels of ethion (0.2% TRR), ethion monooxon (0.2% TRR), ethion dioxon (0.2% TRR), O,O-diethyl-S-(methylsulfinyl) methylphosphoro-dithioate (FMC 78152; 0.2% TRR), and O,O'-diethyl-S[(methylthio)methyl] phosphorodi-thioate (FMC 78153; 0.2% TRR) are found in the kidney. In muscle, ethion and O,O-diethyl phosphate (EOOP) are the major metabolites accounting for as much as 8.4% and 10.6% of the terminal residue. The sodium salt of O,O-diethyl

phosphorothionate (ESOP) is a minor metabolite in muscle accounting for as much as 3.8% of the terminal residue and a trace level of O,O-diethylphosphorodithioic acid (ESSP; 0.5% TRR) is also present. In liver, the predominant metabolite is O,O-diethyl phosphate (EOOP; 41.2% TRR). Minor metabolites found in liver include ethion (0.1% TRR), ethion monooxon (0.4% TRR), ethion dioxon (0.3% TRR), O,O-diethyl-S-(methylsulfinyl) methylphosphorodithioate (FMC 78152; 0.3% TRR), O,O-diethylphosphorodithioic acid (ESSP; 0.7% TRR), the sodium salt of O,O-diethyl phosphorothionate (ESOP; 0.7% TRR), and monoethyl phosphate (MEP; 0.5% TRR). A significant portion of the terminal residue in liver has been characterized as unknowns (25.8% TRR); however, each unknown has been identified as a distinct component that individually accounted for $\leq$7.7% of the terminal residue (MRID#s 00073144, 00155874, 42113702, 42113703, 42113704).

Poultry - The qualitative nature of the residue in poultry is not adequately understood (MRID# 00155875). However, data on the qualitative nature of the residue in poultry is not required for this assessment since citrus is not currently recognized by the Agency as a poultry feed item.

c. Residue Analytical Methods - Plants and Animals

An adequate method for purposes of enforcement of ethion tolerances in plant and animal commodities is available. The GLC/FPD method for determining ethion and ethion monooxon residues as distinct components is described in the Pesticide Analytical Manual (PAM), Vol. II, as Method I. This method is the organophosphate method formerly listed in PAM, Vol. I as multiresidue Protocol II. In this method, acetone extracts of 50-g macerated samples are then extracted twice with methylene chloride, concentrated, mixed with acetonitrile, cleaned up on a polyethylene-coated alumina column, eluted with 60:40 (v:v) acetonitrile and water, extracted with methylene chloride, and analyzed with a gas chromatograph (CG) equipped with a flame photometric detector (FPD). Sensitivity is stated as 0.10 ppm for residues of ethion and ethion monooxon based on a 50 gram sample. Analytical methods deemed adequate by the Agency for data collection were used to generate the citrus field trial data, citrus processing data and meat and milk data submitted in support of the reregistration of ethion (MRID#s 00034468, 00073062,

00073094, 00073100, 00073105, 00073106, 00073141, 00073143, 00073147, 00073173, 00073811, 00073812, 00109285, 00155850, 42411403, 42833401).

PESTDATA (PAM, Vol. I, Appendix II) contains data concerning the applicability of all FDA multiresidue methods for recovery of ethion and ethion monooxon. Ethion is completely recovered (>80%) using PAM Vol. I multiresidue Protocols I, II, and III. Ethion monooxon is completely recovered using Protocols II and III.

Additional data are required as confirmatory information. A representative sample from the goat metabolism study (MRIDs 42113702 through 42113704) must be analyzed using the preferred enforcement method. The Agency has favorably reviewed a protocol submitted by the registrant concerning the conduct of the radiovalidation study.

d. Storage Stability

Adequate storage stability data on ethion residues are available to support the storage conditions and intervals of samples from magnitude of the residue studies on citrus fruits. Residues of ethion and ethion monooxon are stable in/on oranges at -15^{o}C to -25^{o}C for up to 38 months and in/on lemons and grapefruit for approximately 15 months. Storage stability data for the processed commodities of citrus reflecting up to 12 months of storage at -18^{o}C are required to support citrus processing data (MRID 00155850) used for tolerance reassessment. Sample storage conditions and intervals must be reported for the meat and milk magnitude of the residue study (MRIDs 00073138 and 00073153) used for tolerance reassessment. Storage stability data which adequately reflect meat and milk sample storage conditions and intervals are also required. All required data are considered confirmatory since available data indicate that reasonable diligence was exercised in the conduct of the subject studies to ensure that magnitude of the residue results were not invalidated due to sample storage and since existing evidence indicates that residues of ethion and ethion monooxon are relatively stable in unprocessed frozen citrus over long storage intervals (MRID#s 00073152, 00155504, 42411401, 42411402, 42833401).

Additional data are required for storage stability in processed citrus commodities (see below).

e. Magnitude of the Residue in Plants

Data submitted to fulfill this requirement are adequate to reassess the tolerances for residues of ethion in/on citrus fruits. The use of ethion on citrus grown in Florida and Texas only is supported by acceptable field residue data from trials reflecting the maximum registered use pattern. The submitted citrus field trial data indicate that the current tolerance level for ethion residues of concern in/on citrus fruits should be increased to 5 ppm (MRID#s 00073143, 00155580, 00155850, 42411407, 42411408, 42833401 42411409, 42411410, 42411411, 42411412, 42411404, 42411405, 42411406).

f. Magnitude of the Residue in Processed Food/Feed

Data submitted to fulfill this requirement are adequate to determine the extent to which residues of ethion concentrate in processed citrus products (MRID# 00155850). An adequate citrus processing study indicates that the combined residues of ethion and ethion monooxon concentrate up to 10.8 times in citrus oil and 4.3 times in dehydrated citrus pulp processed from ethion-treated fruit (MRID# 00155850). Consequently, HED has recommended that the established tolerance in dehydrated citrus pulp be increased from 10 to 25 ppm and that a tolerance be established in citrus oil at 55 ppm. Pending submission of acceptable storage stability data on processed citrus commodities, no additional data are required.

g. Magnitude of the Residue in Meat, Milk, Poultry, and Eggs

Cattle feeding studies were reviewed in the Registration Standard (9/82). Cows were fed ethion at rates of 5.0 ppm, 10.0 ppm, and 20.0 ppm for 30 days. Milk collected from cows fed at 5 and 20 ppm contained ethion residues of <0.005-0.009 ppm and <0.005-0.034 ppm, respectively. Muscle and fat tissue collected from cows fed 20 ppm contained ethion residues of 0.008 ppm and 0.222 ppm, respectively. Ethion residues were nondetectable (<0.005 ppm) in kidney and liver tissues from cattle fed with ethion at all levels and in muscle tissues from cattle fed at 5 and 10 ppm.

Ethion monooxon and dioxon residues were nondetectable (<0.005 and <0.01 ppm, respectively) in milk or tissues from cows fed at all levels (MRID#s 00073138, 00073153, 00155850). Based on the available ruminant feeding study, tolerances on cattle fat (2.5 ppm), meat (2.5 ppm), and meat by-products (1.0 ppm) are too high and should be lowered to 0.2 ppm to be consistent with tolerances established on other ruminant animal commodities. [Note: Tolerances on cattle meat, meat by-products, and fat were established for the use of ethion as a cattle dip in Australia; however, this use has not been supported in reregistration.] Storage stability data to support these data are outstanding. These storage stability data are considered confirmatory since available data indicate that reasonable diligence was exercised in the conduct of the subject studies to ensure that magnitude of the residue results were not invalidated due to sample storage and since existing evidence indicates that residues of ethion and ethion monooxon are relatively stable in unprocessed frozen citrus for long storage intervals. Pending the receipt of adequate storage stability data, the Agency considers the available information adequate to reassess the current tolerances on meat and milk. The Agency has recently reviewed the cattle eartag use and determined that the reassessed meat/milk tolerances will be adequate to cover potential residues arising from this use.

Table 4. Summary of Residues in Meat, Milk, Poultry, and Eggs

Tissue	Residues at Various Feeding Levels (ppm)			Tissue to Feed Ratio
	5 ppm	10 ppm	20 ppm	
Milk	<0.005 - 0.009	Not reported	<0.005 - 0.034	0.0017
Muscle	<0.005	<0.005	0.008	0.0004
Fat	Not Reported	Not Reported	0.222	0.0111
Liver and Kidney	<0.005	<0.005	<0.005	0.00025

Acute anticipated residues for milk were based on PDP monitoring data. Acute anticipated residues for meat were calculated as follows. The only feed item associated with ethion is dried citrus pulp. It can be fed to beef or dairy cattle at up to 20% of the diet (Table 1, OPPTS Guideline 860). To determine the dietary burden for calculating acute anticipated residues for meat, the highest average field trial (HAFT) residue for citrus (5.58 ppm) was multiplied by the concentration factor for dried citrus pulp (4.28) and corrected for percent dry matter (91%).

The dietary burden for estimating residues in meat is thus [(5.58 ppm x 4.28)/0.91] x 0.20 = 5.25 ppm. Tissue to feed ratios were calculated from the dairy feeding study as shown above. Based on the dietary burdens and tissue to feed ratios, anticipated residues for meat are as follows: muscle - 0.002 ppm; fat - 0.058 ppm; and, liver and kidney - 0.001 ppm.

Citrus is not currently recognized by the Agency as a poultry feed item. Therefore, the Agency recommended that the previously established tolerances listed in 40 CFR §180.173 for eggs and poultry meat, meat by-products, and fat be revoked at this time.

h. Residue Reduction

These data were required by the Agency on a variety of commodities while in transit and storage and after cooking, peeling and washing to permit a more accurate assessment of acute exposure resulting from consumption of commodities treated with ethion. The Agency granted a waiver from this data requirement because the use pattern will be restricted to application on citrus only.

i. Confined Rotational Crops

The Agency has granted a waiver from this data requirement because the use pattern will be restricted to application on citrus only. Citrus is not a rotated crop.

j. Field Rotational Crops

Not applicable

2. Dietary Risk Characterization - Food Sources

a. Acute Dietary Risk Estimates

The acute dietary risk assessment was conducted using USDA PDP monitoring data for oranges (1994-1996), orange juice (1997), and milk (1996-1997), and anticipated residues for meat. The number of samples analyzed in the PDP program, percent of samples with detections, and range of detections are summarized below in Table 5.

Table 5. Number of samples analyzed in the PDP program, percent of samples with detections, and range of detections for Ethion

Only data used in the acute dietary risk assessment are shown.

Sample	Year	Number of Samples	Samples with Detections (%detects)	Minimum/ Maximum Value Detected (ppm)	Range of LOD's (ppm)
Oranges	1994	683	24 (3.5%)	0.002-0.047	0.001 - 0.008
	1995	691	5 (0.7%)	0.002-0.002	0.001- 0.008
	1996	518	4 (0.8%)	0.002-0.038	0.001-0.011
Orange Juice	1997	692	69 (9.9%)	0.002- 0.006	0.001- 0.009
Milk	1996	570	0	0	0.001
	1997	727	0	0	0.001

The detectable residues for oranges measured by PDP (maximum of 0.047 ppm) are well below the reassessed tolerance level (5 ppm). This is to be expected because samples analyzed in field trials (i.e. to support the tolerance level) are based on residues in whole fruits (peel plus pulp) whereas sample analyzed by PDP have the peel removed. As noted above under Plant Metabolism, residues in oranges are found primarily in the peel (>99% of total residue).

The maximum PDP detected ethion residue in orange juice was 0.009 ppm. Because citrus juice is considered a blended commodity, all PDP residue values for orange juice were used directly in the probabilistic analysis.

Because no detectable residues were reported by PDP for milk (out of 1297 samples analyzed), and anticipated residue of the one-half the limit of detection was used in the acute dietary exposure analysis. Consistent with emerging policy concerning commodities having all non-detectable residues in monitoring programs, as presented at the TRAC meetings, another dietary exposure analysis was conducted with residues in milk assumed to be negligible (i.e., no ethion residues).

Before being used in the Monte-Carlo exposure analysis, the detectable residues reported by PDP for oranges were adjusted using a statistical model to reflect residues that could be potentially

present in single serving sizes of commodities. This was necessary because PDP analyzes composite samples for residues rather than single servings of commodities.

The basic premise of the statistical model is finding the Log-Normal distribution that describes the residues on commodities that have a significant amount of samples with detectable residues (more than 30). To find the Log-Normal distribution that describes the concentration in single servings, it is necessary to estimate the mean value and the standard deviation for the detects. The mean value of the composite samples equals the mean value of the single serving. A high-end estimate of the standard deviation is then calculated by multiplying the composite sample's standard deviation by the square root of the number of units in the composite. Distributions are then generated using the mean and adjusted standard deviation. A Log-Normal distribution of residue values was assembled for citrus commodities. The next step in completing the assessment was the generation of data points from these distributions for use in the Monte-Carlo assessment. For ethion, 1000 data points were generated. These data points were then fed into the dietary exposure model for risk analysis. Percent crop treated information was incorporated and the ratio between detects and non-detects reported in the PDP reports remained intact.

Two probabilistic (Monte-Carlo) acute dietary exposure analyses were conducted:

- ❏ In the first, PDP data for oranges were translated to all citrus (grapefruit, tangelos, tangerines, lemons, limes and kumquats); PDP data for orange juice were translated to other citrus juices; PDP monitoring data were used for milk (anticipated residue of 0.0005 ppm based on all non-detectable residues);

- ❏ The second analysis was performed in a similar fashion, except that milk was considered to have negligible residues (i.e., no ethion was present).

Results for these three analyses are summarized below in Tables 6a and 6b.

Table 6a. Acute Dietary Exposure and Risk Analysis

PDP data for oranges were translated to all citrus (grapefruit, tangelos, tangerines, lemons, limes and kumquats), PDP data for orange juice were translated to all citrus juices, PDP data were used for milk, and acute anticipated residues were used for meat.

Population	95th Percentile		99th Percentile		99.9th Percentile	
	Exposure mg/kg/d	% of Acute RfD	Exposure mg/kg/d	% of Acute RfD	Exposure mg/kg/d	% of Acute RfD
US Population	0.000037	2.1	0.000070	4.1	0.000138	8.1
Nursing Infants (<1 year old)	0.000018	1.1	0.000090	5.3	0.000471	28
Non-nursing infants (<1 year old)	0.000044	2.6	0.000091	5.4	0.000153	9.0
Children (1-6 years old)	0.000075	4.4	0.000127	7.5	0.000213	13
Children (7-12 years old)	0.000053	3.1	0.000090	5.3	0.000159	9.3
Females (13-19 years old)	0.000033	1.9	0.000057	3.4	0.000116	6.8
Males (13-19 years old)	0.000038	2.3	0.000058	3.4	0.000101	6.0

Table 6b. Acute Dietary Exposure and Risk Analysis

PDP data for oranges were translated to all citrus (grapefruit, tangelos, tangerines, lemons, limes and kumquats), PDP data for orange juice were translated to all citrus juices, and milk was considered to have negligible residues (i.e., no ethion was present), acute anticipated residues were used for meat.

Population	95th Percentile		99th Percentile		99.9th Percentile	
	Exposure mg/kg/d	% of Acute RfD	Exposure mg/kg/d	% of Acute RfD	Exposure mg/kg/d	% of Acute RfD
US Population	0.000034	2.0	0.000066	3.9	0.000133	7.8
Nursing Infants (<1 year old)	0.000015	0.9	0.000085	5.0	0.000427	25
Non-nursing infants (<1 year old)	0.000030	1.8	0.000079	4.6	0.000138	8.1
Children (1-6 years old)	0.000069	4.1	0.000120	7.0	0.000213	13
Children (7-12 years old)	0.000050	2.9	0.000087	5.1	0.000155	9.1
Females (13-19 years old)	0.000031	1.9	0.000055	3.3	0.000106	6.2
Males (13-19 years old)	0.000037	2.2	0.000057	3.4	0.000098	5.8

b. Chronic Dietary Risk Estimates

The chronic dietary risk assessment of ethion was conducted by HED using the DRES system, using food consumption data based on a 1977 - 1979 USDA food consumption survey and the chronic RfD of 0.0005 mg/kg body weight/day. Results are summarized in Table 7.

The exposure and corresponding percent of reference dose based on Anticipated Residue Contribution (ARC) for the overall U.S. population from published uses supported in reregistration are listed below. Chronic anticipated residues for citrus commodities were calculated using either PDP or FDA monitoring data.

Table 7. Chronic Dietary Risk Estimates Based on Anticipated Residues for Reassessed Tolerances (HED DRES analysis)

Subgroup	Exposure(mg/kg/day)	%Reference Dose
U.S. population	0.000044	9
Children (1-6 years)	0.000081	16

FMC Corporation also conducted a chronic dietary exposure assessment for ethion using the DEEM (Dietary Exposure Evaluation Model) software and consumption data obtained from the 1989-1992 USDA Continuing Survey of Food Intake by Individuals (CSFII). Table 8 summarizes results of this analysis. This exposure assessment (Novigen Report Ethion 97-01, No MRID #) has been reviewed by HED and found acceptable (E.Doyle, 2/25/98). Anticipated residues and percent of crop treated data were incorporated into the analysis.

Table 8. Chronic Dietary Risk Estimates Based on Anticipated Residues for Reassessed Tolerances (Novigen DEEM analysis)

Population subgroup	Chronic Dietary Exposure (mg/kg/day)	Percent of Chronic RfD Chronic RfD = 0.0005 mg/kg/d
US Population	0.000037	7
All Infants	0.000032	6
Children 1-6 years	0.000104	21
Children 7-12 years	0.000054	11

The chronic dietary exposure estimates using the DRES (1977 consumption database) or DEEM (1989 consumption database) analysis are in good agreement. Based on the estimated exposures/percent RfD values, the chronic dietary risk posed by ethion does not exceed HED's level of concern; the ARCs for the U.S. population and all population subgroups are well below the Reference Dose. Both of these dietary risk estimates may be high because they are based on residue levels derived from the original use rates (9 lbs a.i./A/year) and not the reduced rates proposed as part of the risk mitigation (5 lbs a.i./A/year) for reregistration.

3. Dietary Exposure - Drinking Water Source

EFED provided estimated environmental concentrations (EECs) for ethion in a memorandum dated 11/13/97 (S. Abel).

a. Groundwater

According to EFED, ethion appears to have a low potential to contaminate shallow groundwater according to an aged mobility study. Monitoring data compiled in EPA's *Pesticides in Ground Water Database (9/92*) indicate no detections in 1613 wells sampled in 9 different states including California and Florida (where the highest use is expected to occur). Later studies conducted and reported to the Office of Water's STORET system did not report finding ethion above the LOD in more than 100 samples collected. LODs ranged from 0.01 to 0.04 ppb. The mobility of ethion's toxicologically significant degradate, ethion monoxon, is unknown at this time. The potential for groundwater contamination (and exposure) from ethion are extremely low.

Using a worst-case scenario for groundwater exposure (Tier 1, *SCI-GROW* model), the groundwater estimated environmental concentration (EEC) is 0.052 ppb.

b. Surface Water

According to EFED, It is not likely that surface water will/would be contaminated by way of dissolved run-off although movement into surface water may occur through erosion and/or spray drift. Because of turf ground cover, erosion is not typically expected to be significant in an orchard environment. Also, spray drift from aerial or air blast application can impact nearby bodies of water and canals. (Based on mitigation submitted by the registrant during the reregistration process, aerial application has been withdrawn as an application method.)

Tier 2 (PRZM 2.3-EXAMS 2.94) EECs have been calculated, results are summarized in Table 9. Citrus grown in Florida was selected as the modeled crop and location.

Table 9. EECs calculated using PRZM-EXAMS model

Crop	Maximum	96 Hour	21 Day	90 Day	Mean
Citrus	25 ppb	15 ppb	9.8 ppb	8.7 ppb	6.6 ppb

EFED noted that the relatively high soil/water partitioning coefficient (Koc up to 22149) of ethion suggests that it will be effectively removed in most surface water source drinking water treatment utilities through primary settling and flocculation/ coagulation followed by settling. Therefore, resulting concentrations of ethion that may reach the consumer tap may be considerably less than those estimated by PRZM-EXAMS.

For chronic exposure, EFED recommended using 1 ppb as the dietary (water) exposure estimate for surface water.

c. Drinking Water Levels of Comparison

Currently, HED uses drinking water levels of comparison (DWLOCs) as a surrogate to capture risk associated with exposure to pesticides in drinking water. A DWLOC is the concentration of a pesticide in drinking water that would be acceptable as an upper limit in light of total aggregate exposure to that pesticide from food, water, and residential uses (if any). A DWLOC may vary with drinking water consumption patterns and body weights for specific subpopulations.

DWLOCs were calculated and compared to model estimates of ethion concentrations in ground and surface water. Based on the acute and chronic dietary exposure estimates presented above, drinking water levels of comparison (DWLOCs) were calculated using the formulas presented below.

$$DWLOC_{acute} = \frac{[\text{acute water exposure (mg/kg/day) x (body weight)}]}{[\text{consumption (L) x } 10^{-3}\ \text{mg/}\mu\text{g}]}$$

where:
acute water exposure (mg/kg/day) = aRfD - acute food exposure (mg/kg/day)

$$DWLOC_{chronic} = \frac{[\text{chronic water exposure (mg/kg/day) x (body weight)}]}{[\text{consumption (L) x } 10^{-3}\ \text{mg/}\mu\text{g}]}$$

where:
chronic H_2O exposure (mg/kg/day) = [RfD - (chronic food exposure) (mg/kg/day)]

The Agency's default body weights and consumption values used to calculate DWLOCs are as follows: 70 kg/2L (adult male), 60 kg/2L (adult female) and 10 kg/1L (child).

Acute DWLOC For the 99.9th percentile dietary (food) exposure level, the acute DWLOC for the US population is 55 ppb and for non-nursing infants less than 1 year it is 12 ppb.

Chronic DWLOC Based on the chronic dietary exposure estimates, the chronic DWLOC for the US population is 16 ppb and for children 1-6 years old it is 4 ppb.

B. Occupational & Residential Exposure/Risk Characterization

1. Occupational and Residential Exposure

This occupational and residential exposure and risk characterization includes risk mitigation previously agreed to by the registrant that reduced the maximum label application rate and proposed mandatory engineering controls for mixing, loading, and applying with airblast equipment.

Ethion is used on citrus to control Citrus Red Mite, Citrus Rust Mite, Six spotted Mite, Texas Citrus Mite, Citrus Whitefly and Blackfly, Snow Scale, Black Scale, Brown Soft Scale, California Red Scale, Chaff Scale, Florida Red Scale, Glover Scale, Purple Scale, and Yellow Scale. End-use product formulations for citrus use consist of emulsifiable concentrates (EC), containing from 8.4% to 81.9% active ingredient.

Applications can be made using ground equipment or aircraft. The registrant has volunteered to prohibit aerial applications as a risk mitigation measure. Maximum application rates were originally 7.5 pounds active ingredient per acre, but the registrant volunteered to reduce the maximum rate to 2.5 pounds active ingredient per acre as a risk mitigation measure. The exposure assessment in this document is, therefore, based on the maximum of 2.5 pounds active ingredient per acre.

Ethion is currently used in ear tags for livestock insect pest control. Ear tags are impregnated with insecticide and applied to the livestock during the fly season, then removed at the end of the fly season. One or two tags may be used. Chemical resistant gloves should be worn when applying the tags (not leather), and caution taken to avoid breathing vapors. No exposure study data is available for ear tags, but occupational exposure is anticipated to be low if gloves are used.

a. Exposure - Mixer/Loader/Applicator

Based on the ethion pattern of use, several exposure scenarios are plausible as defined by the types of application equipment and procedures that might be employed by ethion handlers. The basic tenets in each scenario are put forth in Table 10 (Assumptions Used in Estimating Worker Short and Intermediate-Term Exposure to Ethion) and more fully explained in Table 11 (Exposure Scenario Description for Uses of Ethion). Table 11 summarizes the caveats and parameters specific to each exposure scenario. This table also includes a description of the sources for the exposure data as well as general information pertaining to the techniques used to calculate the corresponding exposure values. The quality of the data for each exposure scenario is also addressed. These assessments include the typical equipment used to treat citrus. Exposure estimates were derived from Pesticide Handler Exposure Database (PHED) Version 1.1. For several scenarios, exposure data were unavailable for the exact personal protective equipment (PPE) requirements necessary for the exposure/risk assessment. As a result, standard protection factors were applied to the available data for those scenarios to adjust the data to represent as closely as possible the necessary PPE scenario. Table 10 indicates the situations where protective factors were used in this assessment.

Table 12 presents the results of the exposure scenarios and the calculated MOEs. The risk estimates corresponding to each exposure scenario were not assessed for the use of open mixing, loading, and application systems and baseline attire, which is long-sleeve shirt, long pants, shoes, and socks and no respirator. Margins of exposure (MOEs) were found to be too low at baseline, indicating a level of concern. Therefore, the exposure estimates and MOEs are reported for worker scenarios using additional personal protective equipment (PPE) or engineering controls. Table 11 utilizes the toxicological endpoints based upon animal studies. The acceptable MOE for these exposure estimates is 100.

b. Studies: Mixer/Loader/Applicator

In the 1989 Registration Standard, mixer/loader/applicator exposure data were required by the Agency because ethion met triggers for the requirement of exposure data (i.e., toxicity endpoint and the potential for significant exposure based on the use pattern). Mixer/loader/applicator (i.e., handler) exposure study requirements are addressed by Subdivision U of the Pesticide Assessment Guidelines. Mixer/loader/applicator (M/L/A) exposure data (i.e., Guideline (GL) #s 231 and 232: outdoor dermal and inhalation, and GL#s 233 and 234: indoor dermal and inhalation), involving several use patterns (terrestrial food, terrestrial non-food, greenhouse non-food, and domestic outdoor) were required by the 1989 *Registration Standard for Products Containing Ethion*. The required data have not been submitted by the registrants. However, because the registrants are maintaining only the citrus use, only data for Guidelines 231 and 232 for citrus are currently required.

A document entitled "Biomonitoring Risk Assessment and Margin of Safety Risk Assessment Based on Surrogate Exposure Models for Workers Treating Citrus with Ethion Insecticide/Miticide in Airblast Sprayers" (EPA MRID 41716001) was submitted to the Agency in support of Subdivision U requirements for the reregistration of ethion. This submission did not meet the acceptability criteria outlined in Subdivision U of the Pesticide Assessment Guidelines.

The Mixer/Loader/Applicator risk assessment is unacceptable because of the following major inadequacies:

- ❏ there was a general lack of organization and references,

- ❏ critical surrogate exposure data used in the risk assessment were not properly documented (i.e., several of the data sources used by the investigator were not available to the Agency for review and/or verification, the amount of chemical handled in the surrogate exposure studies was not verifiable, and data manipulations completed by the investigator were not provided in the report),

- ❏ insufficient pharmacokinetics data were included in the submission, and

- ❏ it appeared the investigators selectively utilized available surrogate exposure data to potentially create a bias in the results of the assessment to decrease the anticipated hazards associated with the targeted uses of ethion.

Table 10: Assumptions Used in Estimating Worker Short and Intermediate-Term Exposure to Ethion

Exposure Scenario (Scenario #)	Application Rate (lb ai/acre)	Daily Acres Treated[a]
Mixer/Loader Exposure		
Mixing/Loading Liquids for Airblast Application (1)	2.5	17
Mixing/Loading Liquids for High Pressure Handwand Application (2)	0.05 lb ai/gal	1000 gal
Applicator Exposure		
Airblast Sprayer (3)	2.5	17
High Pressure Handwand Sprayer (4)	0.05 lb ai/gal	1000 gal
Mixer/Loader/Applicator Exposure		
Backpack Sprayer (5)	0.05 lb ai/gal	40 gal
Low Pressure Handwand (6)	0.05 lb ai/gal	40 gal

[a]Daily acres treated (or gallons applied) values are from EPA HED estimates of acreage (or gallons) that could be treated in a single day for each exposure scenario of concern. The figures take into account the relatively high (250 gal/acre) rate of application, which reduces the amount of acres which can be practically treated in one day. Typical airblast application rates usually cover 20 acres per day, but this was reduced to 17 due to the high volume of spray.

Table 11. Exposure Scenario Descriptions for Uses of Ethion

Exposure Scenario (Number)	Data Source	Standard Assumptions[a] (8-hr work day)	Comments[b]
Mixer/Loader Exposure			
Mixing Liquids (1 and 2)	PHED V1.1	17 acres airblast, and 1,000 gallons for high pressure sprayer	**Baseline:** "Best Available" grades: Hands, dermal, and inhalation acceptable grades. Hands = 53 replicates; Dermal = 25 to 122 replicates; Inhalation = 85 replicates. High confidence in dermal data; high confidence in inhalation data. **PPE:** "Best Available" grades: Hands and dermal acceptable grades. Hands = 59 replicates; Dermal = 25 to 122 replicates. High confidence in dermal and inhalation data. **Engineering Controls:** "Best Available" grades: Dermal and inhalation acceptable grades. Dermal = 16 to 22 replicates; Hands = 31 replicates; Inhalation = 27 replicates. High confidence in dermal and inhalation data. PHED data used for baseline and engineering controls, no protection factors (PFs) were necessary. A 50 percent PF was used for the addition of coveralls (PPE).
Applicator Exposure			
Airblast (3)	PHED V1.1	Acreage: 17	**Baseline:** "Best Available" grades: dermal, hands, and inhalation acceptable grades. Dermal = 32 to 49 replicates; hands = 22 replicates; inhalation = 47 replicates. High confidence in dermal and inhalation data. **PPE:** "Best Available" grades: dermal and hands acceptable grades. Dermal = 32 to 49 replicates; hands = 18 replicates. High confidence in dermal data. **Engineering Controls:** "Best Available" grades: dermal and hand acceptable grades; inhalation grades A,B,C. Dermal = 20 to 30 replicates, hands equal 20 replicates; Inhalation = 9 replicates. High confidence in dermal and low confidence in inhalation data. “No glove” data not available. PHED data used for baseline and engineering controls, no PFs were necessary. A 50 percent PF was used for the addition of coveralls (PPE).

Exposure Scenario (Number)	Data Source	Standard Assumptions[a] (8-hr work day)	Comments[b]
High Pressure Handwand Sprayer (4)	PHED V1.1	1,000 gallons	**Baseline:** "Best Available" grades: Hands, dermal, and inhalation all grades. Hands = 2 replicates; Dermal = 9 to 11 replicates; Inhalation = 11 replicates. Low confidence in dermal and inhalation data. **PPE:** "Best Available" grades: Hands and dermal all grades. Dermal = 9 to 11 replicates; hands = 9 replicates. Low confidence in dermal data. PHED data used for baseline, no PFs were necessary. A 50 percent PF was added for coveralls for PPE.
Mixer/Loader/Applicator			
Backpack Sprayer (5)	PHED V1.1	40 gallons	**Baseline:** "Best Available" grades: Hands and dermal grades A, B, C; Inhalation acceptable grades. Hands = 11 replicates; Dermal = 9 to 11 replicates; Inhalation = 11 replicates. Low confidence in dermal and inhalation data. **PPE:** See Baseline. PHED data used for baseline, no PFs were necessary (baseline includes gloves, a no glove scenario is not available). A 50% PF was used for the addition of coveralls (PPE).
Low Pressure Handwand (6)	PHED V1.1	40 gallons	**Baseline:** "Best Available" grades: Hands, dermal, and inhalation all grades. Dermal = 25 to 96 replicates; Hands = 70 replicates; Inhalation = 90 replicates. Low confidence in dermal and inhalation data. **PPE:** "Best Available" grades: Hands acceptable grades, dermal all grades. Dermal = 25 to 96 replicates; Hands = 15 replicates. Low confidence in dermal data. PHED data used for baseline, no PFs were necessary. A 50% PF was used for the addition of coveralls (PPE).

a Standard Assumptions based on an 8-hour work day as estimated by EPA/HED. BEAD data were not available.

b "Best Available" grades are defined by EPA/HED SOP for meeting Subdivision U Guidelines. Best available grades are assigned as follows: matrices with grades A and B data and a minimum of 15 replicates; if not available, then grades A, B, and C data and a minimum of 15 replicates; if not available, then all data regardless of the quality and number of replicates. Data confidence are assigned as follows:High = grades A and B and 15 or more replicates per body part
Medium = grades A, B, and C and 15 or more replicates per body part
Low = grades A, B, C, D, and E or any combination of grades with less than 15 replicates

Table 12: Summary of Exposure and Margins of Exposure Values for Ethion: Short- and Intermediate-Term, Based on Animal Toxicity Endpoints

Exposure Scenario (Scenario #)	Additional PPE[d]							Engineering Controls[e]						
	Dermal Unit Exposure (mg/lb ai)	Inhalation Unit Exposure (ug/lb ai)	Daily Dermal Dose (mg/kg/day)	Dermal MOE[a]	Daily Inhalation Dose (mg/kg/day)	Inhal-ation MOE[b]	Total MOE[c]	Dermal Unit Exposure (mg/lb ai)	Inhalation Unit Exposure (ug/cm2)	Daily Dermal Dose (mg/kg/day)	Dermal MOE[a]	Daily Inhalation Dose (mg/kg/ day)	Inhal-ation MOE[b]	Total MOE[c]
Mixer/Loader Risk														
Mixing/Loading Liquids for Airblast Application (1)	0.017	0.24	0.010	80	1.5 E-4	330	64	0.0086 (gloves)	0.083	5.5 E-3	145	4.9 E-5	1020	130
Mixing/Loading Liquids for High Pressure Handwand (2) Application			0.012	67	1.7 E-4	290	54			0.006	130	6.0 E-5	830	110
Applicator Risk														
Airblast Sprayer (3)	0.22	0.9	0.13	6	5.4 E-4	93	5.6	0.019 (gloves)	0.45	0.012	67	2.7 E-4	190	50
High Pressure Handwand (4)	0.36	16	0.26	3.1	0.011	4.5	1.8	None	None	None	None	None	None	None
Mixer/Loader/Applicator Risk														
Backpack Sprayer (5)	1.6	6	0.046	18	1.7 E-4	290	17	None	None	None	None	None	None	None
Low Pressure Handwand (6) [g]	0.37	6	0.011	73	1.7 E-4	290	58	None	None	None	None	None	None	None

None = Engineering Controls are not feasible.

[a]Dermal MOE = Dermal NOAEL (0.8 mg/kg/day)/Daily Dermal Dose

[b]Inhalation MOE = Oral NOAEL (0.05 mg/kg/day) / Daily Inhalation Dose

[c] Total MOE = 1/[1/Dermal MOE + 1/Inhalation MOE]; combined MOEs based upon common toxicological endpoints; acceptable MOEs = 100.

[d]Additional PPE represents coveralls over long pants, long sleeve shirt, chemical resistant gloves, and half face dust/mist respirator using open mixing systems and open cab tractors.

[e]Engineering controls represent single layer clothing; no gloves (except as noted); and no respirators using closed mixing/loading and enclosed cab tractor.

c. Post-Application Exposure

Post-application exposure (i.e., reentry) study requirements are addressed by *Series 875 Occupational and Residential Exposure Test Guidelines: Group B Post-application Exposure Monitoring Test Guidelines*. Post-application dermal and inhalation exposure monitoring along with concurrent soil and foliar residue dissipation data were required in the 1989 *Registration Standard for Products Containing Ethion*. Data for several use patterns were required including terrestrial food, terrestrial non-food, greenhouse non-food, and domestic outdoor. The required data have not been submitted by the registrant. Since use on citrus is the only use being supported in reregistration, only those data pertaining to this terrestrial food use are still required.

A document entitled "Margin of Safety Risk Assessment Based on Surrogate Exposure Models for Workers Reentering Citrus Treated With Ethion Insecticide/Miticide, Revision No. 1" (EPA MRID 415089-01) was submitted to the Agency in support of Subdivision K requirements for the reregistration of ethion. The risk assessment is unacceptable because of several major inadequacies, including:

- ❏ there was a general lack of organization and references,

- ❏ critical data used in the risk assessment were not properly documented (i.e., the data source used by the investigator was not available to the Agency for review and/or verification, no meteorological data were reported, not storage stability data were reported, only summary data were presented - no raw data)

Based on the toxicological endpoints and the potential for reentry exposure, the following data are required for reregistration:

- ❏ GL# 132-1(a). Foliar dislodgeable dissipation: Data are required for Orchard type crops (at least one representative site, i.e., oranges).

(1) Restricted Entry Interval (REI)

Even though the DFR study was classified as unacceptable, the data from this submission (MRID No. 41508901) were used in estimating an interim restricted entry interval, to remain in effect until the required reentry exposure data are submitted and evaluated. Based on the toxicological database re-evaluation (refer to Dose Response section) and the reduced maximum application rate (2.5 lb a.i./A), dislodgeable foliar residue data from the above-mentioned study, and an estimated transfer coefficient for citrus harvesting of 10,000 cm^2/hour, post-application exposures were estimated beginning with the day of treatment when sprays had dried (12-hour restricted-entry interval) through several subsequent days.

The dislodgeable foliar residues (DFRs) are calculated based on regression data using the data from the above ethion study. The study monitored for both ethion and its primary degradate, ethion oxon (more specifically total dioxon plus monooxon). Since no toxicity endpoint is available for the ethion oxon, the NOAEL (LOAEL for ethion) was assumed for both. As noted earlier under I. Hazard Assessment, 12. Other Toxicological Considerations, in general, oxons are *more* toxic than the parent compound.

All analyses are completed using the ethion DFR data and the total DFR data (i.e., cumulative ethion and oxon DFRS). The study was based on 3.0 pounds active ingredient per acre, but current maximum rates are 2.5 pounds active ingredient per acre. Therefore, the DFRS have been normalized using a simple linear proportion to adjust for the lower rate. This procedure is atypical for normal risk assessment practices and should be considered as an uncertainty during assessment of the calculations.

Potential average daily dose (ADD) is calculated as follows:

$$\text{Potential ADD} = \frac{\text{DFR } (\mu g/cm^2) \times \text{Transfer Coefficient } (10{,}000\ cm^2/hr) \times \text{Work Day } (8\ hr)}{\text{Unit Adjustment from ug to mg } (1000\mu g) \times \text{Body Weight } (70\ kg)}$$

The animal toxicity based estimated doses do not utilize the dermal

absorption factor because the endpoint is derived from a dermal study.

Table 13. Restricted-Entry Intervals for Citrus[a]

Time After Treatment	Best Fit DFR (ug/cm$^{2)}$)		Transfer Coefficient (cm^2/hr)	Body Weight (kg)	Daily Work Hours	Potential Daily Exposure (mg/kg/day)[c]		MOE Calculations[d]	
								Animal Endpoints	
	Ethion Only	Total: Ethion + Oxon[b]				Ethion Only (X 10^{-2})	Total: Ethion + Oxon[b] (X 10^{-2})	Ethion Only	Total: Ethion + Oxon
12 hours	0.078	0.086	10,000	70	8	8.9	9.8	9.0	8.2
1 day	0.056	0.063	10,000	70	8	6.4	7.2	13	11
2 days	0.040	0.048	10,000	70	8	4.5	5.3	18	15
3 days	0.028	0.034	10,000	70	8	3.2	3.9	25	21
4 days	0.020	0.025	10,000	70	8	2.3	2.8	35	29
5 days	0.014	0.018	10,000	70	8	1.8	2.1	44	38
6 days	0.010	0.013	10,000	70	8	1.2	1.5	67	53
7 days	0.0080	0.011	10,000	70	8	0.90	1.2	89	67
8 days	0.0054	0.0075	10,000	70	8	0.62	0.86	130	93
9 days	0.0039	0.0055	10,000	70	8	0.45	0.63	180	130

[a]The study was conducted at a higher application rate than 2.5 lb ai/acre. The exposure values have been corrected to this lower rate and are reflected in the MOEs above. The lower rate of 2.5 lb ai/acre was proposed as a maximum rate proposed during this reregistration process as a mitigation measure. A best-fit regression line was computed from the DFR data and used to extrapolate in order to obtain a re-entry interval with an MOE over 100.

[b]Oxon represents the total of the monooxon plus the dioxon.

[c]Potential ADD = [DFR (ug/cm^2) X Transfer Coefficient (10,000 cm^2/hr) X Work Day (8 hr)] / [Unit Adjustment from ug to mg (1000ug) X Body Weight (70 kg)]

[d]MOE [animal data] = Dermal NOAEL (0.8 mg/kg/day)/Daily Dermal Dose; MOE [human data] = LOAEL (0.05 mg/kg/day)/Daily Dermal Dose

NC: Not calculated

d. Residential Exposure

All residential uses for ethion have been voluntarily canceled by the registrant.

2. Occupational and Residential Risk Characterization

a. Incidents Reported

Ethion has been cited in numerous pesticidal poisoning incidents. In California in 1970s, a worker restricted-entry interval of 30 days was established as a result of serious incidents reported among workers entering fields previously treated with ethion. California Department of Food and Agriculture reported one incident of ethion poisoning in 1981. There were 7 poisoning incidents in 1983. These cases involved field workers re-entering treated fields in 1983, a year with 812 reported applications of ethion. For perspective, ethion was the 8th most frequent cause of re-entry poisonings in California during the period 1976-85. There were no reported ethion poisonings in 1987 and 1988. Two incidents were reported in 1989, 1 eye and 1 skin adverse reaction. Use of ethion in California declined steadily during the 1980's from a peak of 1027 applications in 1984, to 35 applications in 1991. Use was reportedly discontinued in California to prevent further poisonings to field workers entering treated fields.

EPA's Incident Data System (IDS) contains information on adverse reactions to ethion; for the reporting period of April 1992 to July 1993, three data entries contained a total 116 incidents. Most of the incidents pertain to humans, but some include cattle and domestic animals.

The National Pesticide Telecommunication Network reports from 1984-1991 inclusive, show 20 human poisoning incidents and 1 animal poisoning incident, and 3 rated other, among 73 calls to the EPA hotline.

Ethion was not included in the "Acute Worker Risk Strategy, therefore there are no data available from the American Association of Poison Control Centers, at this time.

b. Handler Risk Estimates

Dermal MOEs are a ratio of the dermal NOAEL of 0.8 mg/kg/day to dermal exposure. The inhalation MOEs are all calculated using 0.05 mg/kg/day and 100% absorption. The Margins of Exposure (MOE) are summarized in Table 12 (details) or below in Table 14.

For short and intermediate-term exposure based on animal study endpoints:

Total MOE = 1/[1/Dermal MOE + 1/Inhalation MOE];
combined MOEs based upon common toxicological endpoints;
acceptable MOEs = 100.

For ethion, an MOE of greater than 100 is not considered a risk concern.

The exposure data for estimating the risk to mixer/loaders (airblast, aerial, and high pressure handwand) is based on high quality data for baseline, additional protection equipment and engineering controls. The applicator risk for airblast applications is based on high quality exposure data for the three levels of protection. The risk for the remainder of the scenarios (backpack, low pressure handwand and high pressure handwand) is based on low quality data and we have low confidence in the exposure and risk estimate.

The MOEs with baseline attire are less than 100 in every exposure scenario where data are available. No data are available for backpack sprayers at baseline attire.

The MOEs calculated using animal toxicity data based endpoints, all remain lower than 100, or above the level of concern. Again using animal data, and adding engineering controls to baseline attire, the MOEs for mixing and loading airblast and hand wand application were acceptable, but airblast application was not. No feasible engineering controls are available for high-pressure handwand application, low-pressure handwand mixing/loading/applying, or backpack sprayer mixing/loading/applying, so those exposure scenarios remain a level of concern.

A chronic occupational exposure scenario has not been identified for this chemical; therefore, a chronic (noncancer) risk assessment was not conducted.

Table 14. Summary of Occupational Risk Estimates with Additional Mitigation

Scenario	Animal Toxicity Endpoints: Baseline Plus PPE	Animal Toxicity Endpoints: Engineering Controls[b]
Total Risk Method[a]	MOE [100]	MOE [100]
M/L: Airblast	64	130*
Applicator: Airblast	5.6	50*
M/L/A: Airblast	5.3	36*
M/L: HP Handwand	54	110
Applicator: HP Handwand	1.8	None
M/L/A: LP Handwand	58	None
M/L/A: Backpack Sprayer	17	None

[a]An MOE of less than 100 is considered a risk concern. The exposure estimates in these MOE determinations are based on the lowest proposed application rate as a mitigation measure of 2.5 lb ai/acre (versus 7.5 lb ai/acre currently reflected on labels).
[b]Engineering controls represent single layer clothing; no gloves (unless indicated with *); and no respirators using closed mixing/loading, and enclosed cab tractor.

c. Post-Application Risk Estimates

MOEs are calculated for post-application risks as follows:

$$MOE = \frac{NOAEL\ (mg/kg/day)}{Absorbed\ ADD\ (mg/kg/day)}$$

Table 13 presents the MOEs for citrus ranging from the day of application after sprays have dried (MOEs of 17 and 15) to 7 days after application when the MOE exceeds 100 for total foliar dislodgeable residues (DFR) values. MOEs of less than 100 are considered a risk concern. The transfer coefficient (Tc) was estimated based on the reasonable worse-case task of harvesting citrus. The DFRs were corrected for the lower application rate (2.5 lb ai/acre) since the study was conducted at a slightly higher rate. DFR data from the citrus studies were chosen by EPA as the best available DFR data but it should be noted that the foliar dislodgeable residue levels were combined for the assessment in a

manner which is technically unacceptable i.e combined dry and wet season data to obtain representative levels. The MOE, *based on the toxicity endpoint for the ethion parent only,* for post-application exposures reaches 100 for total exposure (ethion plus oxon) at day 6 following application. However, the acute toxicity of the ethion-oxon(s) may be 2-3 times that of the parent and possibly as much as 10 times. Considering the degradation rate of ethion to the oxon(s) and the toxicity of the oxon(s) as compared to the parent an REI of 6 may result in an excessive risk to the worker. This must be tempered for the limitations on the foliar dislodgeable residue levels used. Taking into account the incidents in California and until adequate toxicity data are available to appropriately assess the risk to workers from the oxon(s) and quantify an REI, an REI of not less than 8 days is recommended. Upon receipt and review of the data requested to determine the toxicity of the ethion oxon(s) the adequacy of the REI will be reevaluated.

Table 15. Summary of Margins of Exposure for Restricted-Entry Intervals for Citrus

Time after Treatment	MOE Calculations	
	Ethion Only	Total: Ethion + Oxon[2]
12 hours	9.0	8.2
1 day	13	11
2 days	18	15
3 days	25	21
4 days	35	29
5 days	44	58
6 days	67	53
7 days	89	67
8 days	130	93
9 days	180	130

[1]The study was conducted at a higher application rate than 2.5 lb ai/acre. The exposure values have been corrected to this lower rate and are reflected in the MOEs above. An MOE of greater than 100 is NOT considered a risk concern.
[2]Oxon represents the total, monooxon plus dioxon.

III. Aggregate Risk Estimates

A. Acute Aggregate Risk Estimates

Acute aggregate risk estimates do not exceed HED's level of concern. Acute aggregate risk estimates are derived using the combined dietary (food and water) exposure. Acute dietary food exposure has been highly refined using probabilistic techniques (Monte-Carlo), residue values derived from the USDA Pesticide Data Program (for citrus and milk), anticipated residues (for meat), and incorporation of percent crop treated data. Food exposure estimates are based on exposure at the 99.9th percentile. For the US population, the highest percent of the acute RfD occupied is 8%. For this exposure analysis PDP data for oranges were translated to all citrus (grapefruit, tangelos, tangerines, lemons, limes and kumquats), PDP data for orange juice were translated to all citrus juices, PDP data for milk were used, and acute anticipated residues were used for meat. If PDP data for oranges, translated to all citrus (grapefruit, tangelos, tangerines, lemons, limes and kumquats) and negligible residues are assumed for milk (based on all non-detectable residues), then the percent of the acute RfD occupied is also 8%. Similarly, for non-nursing infants less than one year old (the most highly exposed sub-population) and these two exposure scenarios, the percent of the acute RfD occupied is 28% and 25% respectively.

Based on Environmental Fate and Effect Division (EFED) Tier 1 modeling for groundwater (SCI-GROW), the estimated environmental concentrations (EECs) for groundwater is 0.05 ppb. Based on Tier 2 (PRZM-EXAMS) surface water modeling, the maximal (day 0) EEC for ethion in surface water is 25 ppb. This conservative modeling estimate does not exceed the drinking water level of comparison (DWLOC) for the US population (which is 55 ppb). However, the calculated DWLOC for non-nursing infants less than one year old is 12 ppb. EFED noted that the relatively high soil/water partitioning coefficient of ethion suggests that it will be effectively removed in most surface water source drinking water treatment utilities through primary settling and flocculation/coagulation followed by settling. Therefore, resulting concentrations of ethion that may reach the consumer tap may be considerably less than those estimated by PRZM-EXAMS. HED thus concludes that acute aggregate exposure to ethion does not exceed our level of concern.

B. Short- and Intermediate-Term Aggregate Risk Estimates

Because there are no registered uses for ethion that could result in residential exposures, short- and intermediate-term aggregate risk assessments are not required.

C. Chronic Aggregate Risk Estimates

Chronic aggregate risk estimates are derived using the combined dietary (food and water) exposure. Chronic dietary food exposure has been highly refined using anticipated residues and percent crop treated data. Partially refined (Tier 2, PRZM-EXAMS) EECs have been calculated for surface water. Tier 1 (SCI-GROW) EECs have been calculated for groundwater.

Based on toxicological endpoints from the animal toxicity studies, chronic dietary exposure from food alone does not exceed HED's level of concern. The percent of the chronic RfD occupied from chronic food exposure alone ranges from 6% for the US Population to 16% for children 1-6 years old. The chronic DWLOC for the US population is 16 ppb and for children it is 4 ppb. EFED recommended that 1 ppb be considered the chronic exposure level for ethion residues in surface water. For groundwater, the tier 1 EEC was 0.05 ppb. HED thus concludes that chronic aggregate exposure to ethion does not exceed our level of concern.

IV. Tolerance Reassessment

Tolerances for the combined residues of the insecticide ethion (O,O,O`,O`-tetraethyl S,S`-methylene bisphosphorodithioate) including its oxygen analog (S-[[(diethyl phosphinothioyl)thio] O,O-diethyl phosphorothioate)listed in 40 CFR § 180.173 have recently been updated (FR 63 No.9, 1/14/98 and FR 63 No.263, 10/26/98). A reassessment of these tolerances is provided.

The Agency has determined that sufficient data are available to ascertain the adequacy of the established tolerances listed in 40 CFR § 180.173 for citrus fruits. The Agency recommends that the tolerance expression for citrus fruits be revised to specify a regional registration and that the tolerance be increased from 2 ppm to 5 ppm.

The Agency has determined that, pending the receipt of storage stability data, data are sufficient to ascertain the adequacy of the established tolerance for dehydrated citrus pulp and to establish a tolerance for citrus oil. The Agency recommends that the currently established tolerance for citrus, pulp, dried be increased from 10 ppm to 25 ppm. The Agency recommends that a tolerance for citrus oil be established at 55 ppm.

The Agency has determined that, pending receipt of test sample storage information and supporting storage stability data, sufficient data are available to ascertain the adequacy of the established tolerances listed in 40 CFR § 180.173 for the fat, meat, and meat byproducts of cattle, goats, hogs, horses, and sheep and milk fat. Based on an available ruminant feeding study, the Agency recommends that tolerances for cattle fat, meat, and meat byproducts should be lowered to 0.2 ppm to be consistent with tolerances established for other ruminant animal commodities.

The Agency recommends that the established tolerances listed in 40 CFR § 180.173 should be revoked for dried tea and raisins. No uses on these commodities are currently registered and the registrant does not intend to support these uses.

Table 16. Tolerance Summary

Commodity	Current Tolerance (ppm)	Tolerance Reassessment (ppm)	Comment/Correct Commodity Definition
Tolerances listed under § 180.173			
Cattle, fat	2.5	0.2	Lower tolerance level needed (a)
Cattle, meat (fat basis)	2.5	0.2	Lower tolerance level needed (a)
Cattle, mbyp	1.0	0.2	Lower tolerance level needed (a)
Citrus, fruits	2.0	5	Higher tolerance level needed
Citrus, oil	N/A	55	New tolerance needed (Pending receipt of adequate storage stability data).
Citrus, pulp, dehydrated	10	25	Increase in tolerance needed (Pending receipt of adequate storage stability data).
Dried tea	10	Revoke	No registered uses exist
Goats, fat	0.2	0.2	(a)
Goats, meat	0.2	0.2	(a)
Goats, mbyp	0.2	0.2	(a)
Hogs, fat	0.2	0.2	(a)
Hogs, meat	0.2	0.2	(a)
Hogs, mbyp	0.2	0.2	(a)
Horses, fat	0.2	0.2	(a)
Horses, meat	0.2	0.2	(a)
Horses, mbyp	0.2	0.2	(a)
Milk fat	0.5(N)	0.5	The designation for negligible (N) residues should be deleted (a)
Raisins	4	Revoke	No registered uses exist
Sheep, fat	0.2	0.2	(a)
Sheep, meat	0.2	0.2	(a)
Sheep, mbyp	0.2	0.2	(a)

(a)Pending the receipt of adequate sample storage information and supporting storage stability information.

V. Data Requirements

A. Residue Chemistry

1. Analytical Method

Additional data are required as confirmatory information. A representative sample from the goat metabolism study (MRIDs 42113702 through 42113704) must be analyzed using the preferred enforcement method. The Agency has favorably reviewed a protocol submitted by the registrant concerning the conduct of the radiovalidation study.

2. Storage Stability

Pending submission of acceptable storage stability data on processed citrus commodities, no additional data are required.

B. Occupational Exposure

1. Mixer/Loader/Applicator

Based on the toxicological endpoints (ChE inhibition), the potential for exposure, and the results of the risk assessments presented above, ethion continues to meet EPA's criteria for the requirement of mixer/loader/applicator exposure data. The following data are required for reregistration:

❏ GL# 231 and 232: Estimation of dermal and inhalation exposures at outdoor sites: Data are required for high-pressure handwand, knapsack/backpack, and low-pressure handwand application to citrus.

2. Post-Application Exposure

Based on the toxicological endpoints and the potential for reentry exposure, the following data are required for reregistration:

❏ GL# 132-1(a). Foliar dislodgeable dissipation: Data are required for Orchard type crops (at least one representative site, i.e., oranges).